PTO Form 1930 (Rev 9/2007)
OMB No. 0651-0050 (Exp. 4/30/2009)

Request for Reconsideration after Final Action

The table below presents the data as entered.

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SERIAL NUMBER	85008626
LAW OFFICE ASSIGNED	LAW OFFICE 101
MARK SECTION (no change)	
ARGUMENT(S)	

SCENT

This Request for Reconsideration is in response to the Final Action from the Examining Attorney, dated October 4, 2011. Applicant respectfully requests withdrawal of the refusal to register and responds as follows:

INFORMALITIES

1. Notice of Appeal

In addition to this communication, Applicant also has filed a Notice of Appeal with the Trademark Trial and Appeal Board, dated April 4, 2012.

REMARKS

1. Failure to Function as a Mark

The Examining Attorney continues to maintain his refusal of Applicant's Mark under Lanham Act Sections 1, 2 and 45, 15 U.S.C. §§ 1051-1052, 1127, asserting that Applicant's Mark fails to function as a trademark. Applicant respectfully disagrees and reiterates that its Mark does function as source-identifier for the goods and has acquired distinctiveness. Applicant respectfully requests that the Examiner reconsider his findings.

The Examiner maintains that evidence showing five (5) years' substantially exclusive use is insufficient to show acquired distinctiveness and that Applicant's length of use is not dispositive on the issue of distinctiveness. See Office Action, pg. 3. However, Applicant has been using its Mark for

much longer than five (5) years. In fact, Applicant has used its Mark substantially exclusively with nitroglycerin pharmaceuticals for nearly twenty-three (23) years. While Applicant acknowledges that five (5) years of use *alone* would be insufficient to prove acquired distinctiveness, Applicant maintains its extremely long use, coupled with Applicant's other *actual* evidence that the Mark is perceived as a trademark for nitroglycerin pharmaceuticals, is a substantial factor. See TMEP Section 1212.05(a). In the past twenty-three (23) years, Applicant has educated the public to associate its Mark with a single source (itself) through its extensive and substantially exclusive use.

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attaches hereto a copy of the complaint as **Exhibit B.** The parties subsequently settled. As Applicant asserted with its prior office action response, a late-comer's imitation of a Mark and product merely reinforce that Applicant's Mark has secondary meaning in the marketplace. See, e.g., Parker Laboratories Inc. v. Pharmaceutical Innovations Inc., 20 U.S.P.Q.2d 1152 (S.D.N.Y. 1991) (holding trade dress for plaintiff's "Aquasonic 100" ultrasound transmission gel acquired secondary meaning, in light of volume, extent, and duration of plaintiff's advertising and promotion, and in light of defendant's blatant copying of trade dress).

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The Examiner suggests that such advertising is merely indicative of an effort to develop distinctiveness and not that the Mark has actually acquired distinctiveness. However, millions of buyers and prospective buyers have had *widespread* exposure to this advertising for more than two decades, resulting in millions of commercial impressions throughout the world. As a result of the success of its marketing efforts, Applicant has a 97% share of the nitroglycerin sublingual pharmaceutical market in

the United States. Prior to the recent introduction of Nitromist, Applicant had 100% of the market share in the United States. In other countries, such as Australia, Applicant continues to occupy a 100% market share.

The Examining Attorney maintains that the mark that figures in Applicant's advertising is Nitrolingual®, not the applied-for Mark, and that the Mark will be perceived only as an intrinsic feature of the pharmaceutical. However, Applicant has provided with prior office action responses *actual* evidence that relevant purchasers (e.g. healthcare professionals) do, in fact, view the scent as a trademark and associate the scent with Applicant and Applicant's brand. See, e.g., Boehringer Ingelheim G.m.b.H. et al. v. Pharmadyne Laboratories, Inc. et. al, 211 U.S.P.Q. 1163, 1184 (D.N.J. 1980) (finding recognition by physicians and pharmacists "*highly persuasive*" evidence of secondary meaning).

The Examiner discredits the declarations, calling the conclusions in the letters "suspect," without basis, and stating that the probative value of the twenty-six letters is "very limited" given their form format. See Office Action, pgs. 4-5. However, form format letters are competent evidence of secondary meaning, and the fact that the letters are in form format does not make the statements contained within them any less true. See, e.g., In re Black & Decker Corp., 81 U.S.P.Q.2d 1841 (T.T.AB. 2006) (finding applicant's ten form letters, similar to the ones at hand, in support of its claim of acquired distinctiveness were "*competent evidence*" of consumer recognition as a trademark, despite Examiner's assertion that letters were unpersuasive).

Here, the Examiner also maintains that none of the letters provide information as to the qualifications of the individuals making the statements or any " basis" for the conclusions. Office Action, pgs. 4-5. However, the letters clearly state the individuals' names and titles, indicate that they have been "treating patients for angina pectoris" for "years," that they have "become very familiar with different pharmaceutical formulations of nitroglycerin on the market," and they "regularly prescribe" the goods that are covered by this application. Similar language was used in the declarations in In re Black & Decker Corp., and the T.T.A.B. found "the language [was] clear as to what is understood to represent Applicant's applied-for mark." Id. The declarations that Applicant has submitted with this application are competent and direct evidence that consumers recognize Applicant's Mark as a trademark and that the peppermint scent do indeed function as source indicators.

In support of its claim of acquired distinctiveness, Applicant also has provided substantial and impressive revenue figures that are in the hundreds of millions of dollars, and significant sales figures, having sold millions of pharmaceutical units bearing the Mark. The Examiner dismisses these figures, maintaining that they apply to the marketing and sale of Nitrolingual® and that there is insufficient evidence showing the amount of marketing revenues, for instance, that apply to the trade dress. See Office Action, pg. 3. Applicant respectfully asserts that the Examiner's focus on sales and revenue applicable solely to the trade dress is misplaced. Applicant's Mark is part and parcel of a pharmaceutical product sold to consumers. Applicant does not sell the scent *by itself*. It would be impossible to provide sales and revenue figures attributable *solely* to the peppermint scent. Sales success to the extent of Applicant's clearly support the conclusion that the Mark has acquired secondary meaning. Arrow Fastener Co., Inc. v. Stanley Works, 59 F.3d 384, 393, 35 U.S.P.Q.2d 1449 (2d Cir. 1995) (finding sales figures relevant evidence from which to infer the existence of secondary meaning).

CONCLUSION

In light of the foregoing, it is clear that Applicant's Mark functions as a trademark and has secondary meaning in the minds of consumers. Use of a peppermint scent in connection with nitroglycerin is not common in the marketplace and is a unique trademark that consumers clearly associate with Applicant. Applicant has presented competent and substantial evidence in the form of actual consumer testimony and significant sales, revenue and advertising figures, which all supporting a finding of acquired distinctiveness. Accordingly, Applicant submits that registration on the Principal Register is proper and hereby respectfully requests such action.

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SIGNATORY'S POSITION	Attorney of Record Massachusetts Bar Member
SIGNATORY'S PHONE NUMBER	617.261.3224
DATE SIGNED	04/04/2012
AUTHORIZED SIGNATORY	YES
CONCURRENT APPEAL NOTICE FILED	NO
FILING INFORMATION SECTION	

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To the Commissioner for Trademarks:

Application serial no. **85008626** (Sound/Motion Mark) has been amended as follows:

ARGUMENT(S)
In response to the substantive refusal(s), please note the following:

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The Examiner suggests that such advertising is merely indicative of an effort to develop distinctiveness and not that the Mark has actually acquired distinctiveness. However, millions of buyers and prospective buyers have had *widespread* exposure to this advertising for more than two decades,

resulting in millions of commercial impressions throughout the world. As a result of the success of its marketing efforts, Applicant has a 97% share of the nitroglycerin sublingual pharmaceutical market in the United States. Prior to the recent introduction of Nitromist, Applicant had 100% of the market share in the United States. In other countries, such as Australia, Applicant continues to occupy a 100% market share.

The Examining Attorney maintains that the mark that figures in Applicant's advertising is Nitrolingual®, not the applied-for Mark, and that the Mark will be perceived only as an intrinsic feature of the pharmaceutical. However, Applicant has provided with prior office action responses *actual* evidence that relevant purchasers (e.g. healthcare professionals) do, in fact, view the scent as a trademark and associate the scent with Applicant and Applicant's brand. See, e.g., Boehringer Ingelheim G.m.b.H. et al. v. Pharmadyne Laboratories, Inc. et. al, 211 U.S.P.Q. 1163, 1184 (D.N.J. 1980) (finding recognition by physicians and pharmacists " *highly persuasive*" evidence of secondary meaning).

The Examiner discredits the declarations, calling the conclusions in the letters "suspect," without basis, and stating that the probative value of the twenty-six letters is "very limited" given their form format. See Office Action, pgs. 4-5. However, form format letters are competent evidence of secondary meaning, and the fact that the letters are in form format does not make the statements contained within them any less true. See, e.g., In re Black & Decker Corp., 81 U.S.P.Q.2d 1841 (T.T.AB. 2006) (finding applicant's ten form letters, similar to the ones at hand, in support of its claim of acquired distinctiveness were " *competent evidence*" of consumer recognition as a trademark, despite Examiner's assertion that letters were unpersuasive).

Here, the Examiner also maintains that none of the letters provide information as to the qualifications of the individuals making the statements or any " basis" for the conclusions. Office Action, pgs. 4-5. However, the letters clearly state the individuals' names and titles, indicate that they have been "treating patients for angina pectoris" for "years," that they have "become very familiar with different pharmaceutical formulations of nitroglycerin on the market," and they "regularly prescribe" the goods that are covered by this application. Similar language was used in the declarations in In re Black & Decker Corp., and the T.T.A.B. found "the language [was] clear as to what is understood to represent Applicant's applied-for mark." Id. The declarations that Applicant has submitted with this application are competent and direct evidence that consumers recognize Applicant's Mark as a trademark and that the

peppermint scent do indeed function as source indicators.

In support of its claim of acquired distinctiveness, Applicant also has provided substantial and impressive revenue figures that are in the hundreds of millions of dollars, and significant sales figures, having sold millions of pharmaceutical units bearing the Mark. The Examiner dismisses these figures, maintaining that they apply to the marketing and sale of Nitrolingual® and that there is insufficient evidence showing the amount of marketing revenues, for instance, that apply to the trade dress. See Office Action, pg. 3. Applicant respectfully asserts that the Examiner's focus on sales and revenue applicable solely to the trade dress is misplaced. Applicant's Mark is part and parcel of a pharmaceutical product sold to consumers. Applicant does not sell the scent *by itself*. It would be impossible to provide sales and revenue figures attributable *solely* to the peppermint scent. Sales success to the extent of Applicant's clearly support the conclusion that the Mark has acquired secondary meaning. Arrow Fastener Co., Inc. v. Stanley Works, 59 F.3d 384, 393, 35 U.S.P.Q.2d 1449 (2d Cir. 1995) (finding sales figures relevant evidence from which to infer the existence of secondary meaning).

CONCLUSION

In light of the foregoing, it is clear that Applicant's Mark functions as a trademark and has secondary meaning in the minds of consumers. Use of a peppermint scent in connection with nitroglycerin is not common in the marketplace and is a unique trademark that consumers clearly associate with Applicant. Applicant has presented competent and substantial evidence in the form of actual consumer testimony and significant sales, revenue and advertising figures, which all supporting a finding of acquired distinctiveness. Accordingly, Applicant submits that registration on the Principal Register is proper and hereby respectfully requests such action.

EVIDENCE

Original PDF file:
evi_7237171204-135326001_._Exhibit_A-_Scent.pdf
Converted PDF file(s) (5 pages)
Evidence-1
Evidence-2
Evidence-3
Evidence-4
Evidence-5

Original PDF file:
evi_7237171204-135326001_._Exhibit_B-_Scent.pdf
Converted PDF file(s) (83 pages)
Evidence-1
Evidence-2
Evidence-3
Evidence-4
Evidence-5
Evidence-6
Evidence-7
Evidence-8
Evidence-9
Evidence-10
Evidence-11
Evidence-12
Evidence-13
Evidence-14
Evidence-15
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Evidence-80
Evidence-81
Evidence-82
Evidence-83

Original PDF file:
evi_7237171204-135326001_._Exhibit_C-_Scent.pdf

Converted PDF file(s) (7 pages)
Evidence-1
Evidence-2
Evidence-3
Evidence-4
Evidence-5

Evidence-6
Evidence-7
Original PDF file:
evi_7237171204-135326001_._Exhibit_E-_Scent.pdf
Converted PDF file(s) (4 pages)
Evidence-1
Evidence-2
Evidence-3
Evidence-4
Original PDF file:
evi_1-7237171204-135326001_._Exhbit_D_-_Scent.pdf
Converted PDF file(s) (2 pages)
Evidence-1
Evidence-2

SIGNATURE(S)
Request for Reconsideration Signature
Signature: /philan tinsley/ Date: 04/04/2012
Signatory's Name: Phi Lan Tinsley
Signatory's Position: Attorney of Record Massachusetts Bar Member

Signatory's Phone Number: 617.261.3224

The signatory has confirmed that he/she is an attorney who is a member in good standing of the bar of the highest court of a U.S. state, which includes the District of Columbia, Puerto Rico, and other federal territories and possessions; and he/she is currently the applicant's attorney or an associate thereof; and to the best of his/her knowledge, if prior to his/her appointment another U.S. attorney or a Canadian attorney/agent not currently associated with his/her company/firm previously represented the applicant in this matter: (1) the applicant has filed or is concurrently filing a signed revocation of or substitute power of attorney with the USPTO; (2) the USPTO has granted the request of the prior representative to withdraw; (3) the applicant has filed a power of attorney appointing him/her in this matter; or (4) the applicant's appointed U.S. attorney or Canadian attorney/agent has filed a power of attorney appointing him/her as an associate attorney in this matter.

The applicant is not filing a Notice of Appeal in conjunction with this Request for Reconsideration.

Serial Number: 85008626
Internet Transmission Date: Wed Apr 04 13:58:50 EDT 2012
TEAS Stamp: USPTO/RFR-72.37.171.204-2012040413585004
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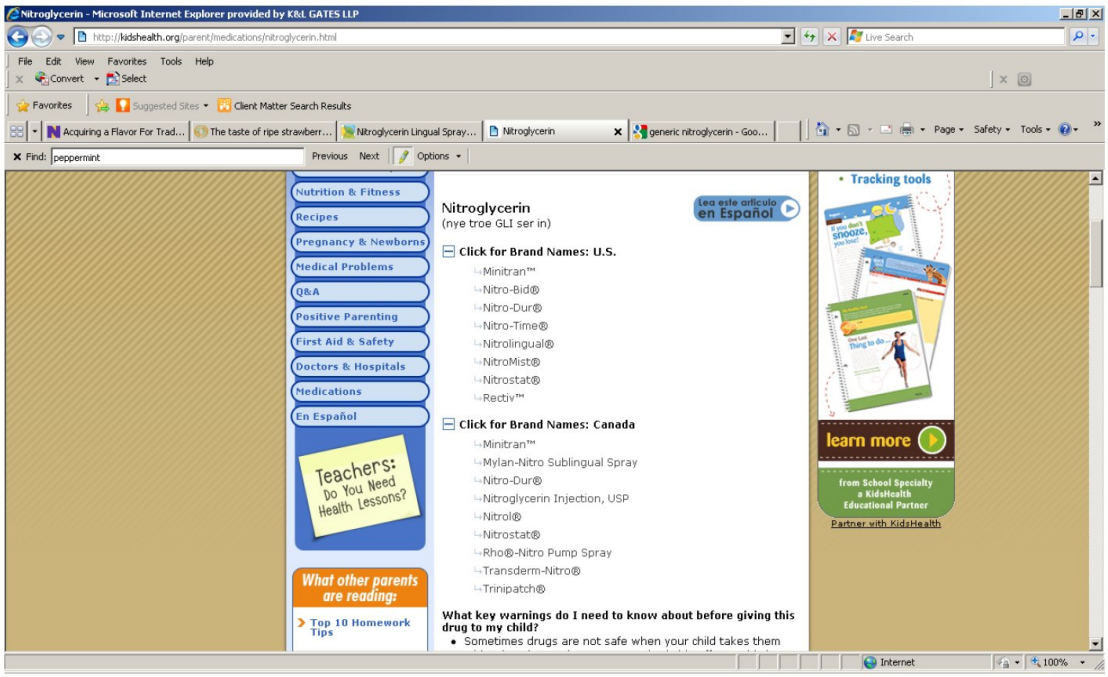
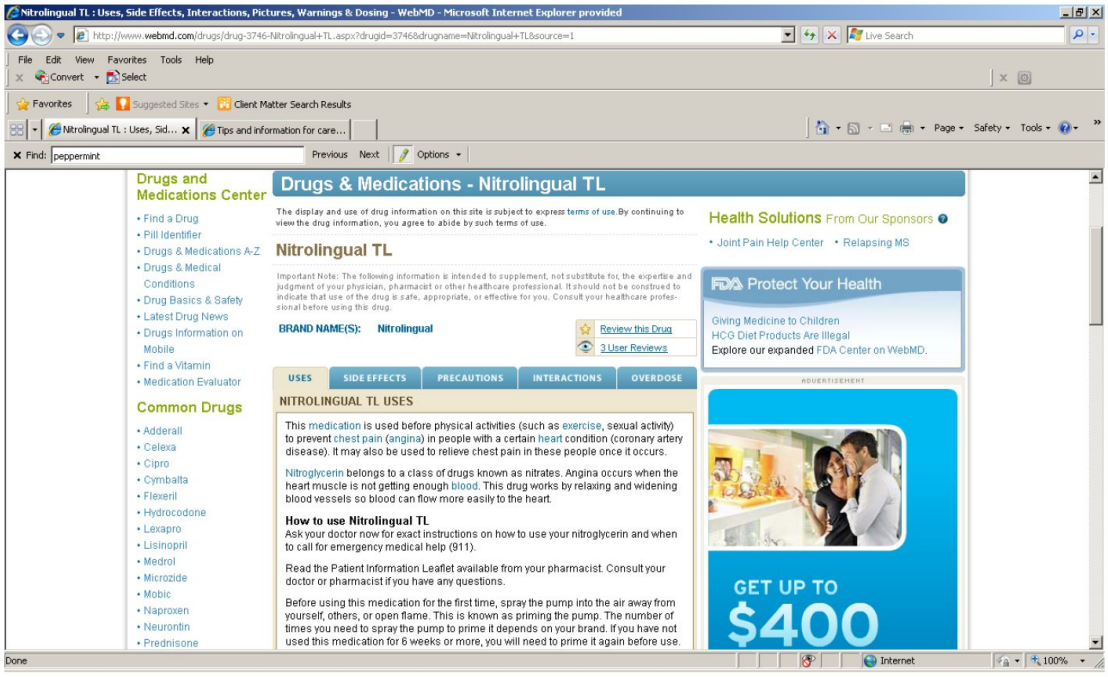
EXHIBIT A


Nitroglycerin - Microsoft Internet Explorer provided by K&L GATES LLP
http://kidshealth.org/parent/medications/nitroglycerin.html
Nutrition & Fitness
Recipes
Pregnancy & Newborns
Medical Problems
Q&A
Positive Parenting
First Aid & Safety
Doctors & Hospitals
Medications
En Español
Teachers: Do You Need Health Lessons?
What other parents are reading:
Top 10 Homework Tips
Nitroglycerin
(nye troe GLI ser in)
Lea este artículo en Español
Click for Brand Names: U.S.
Minitran™
Nitro-Bid®
Nitro-Dur®
Nitro-Time®
Nitrolingual®
NitroMist®
Nitrostat®
Rectiv™
Click for Brand Names: Canada
Minitran™
Mylan-Nitro Sublingual Spray
Nitro-Dur®
Nitroglycerin Injection, USP
Nitrol®
Nitrostat®
Rho®-Nitro Pump Spray
Transderm-Nitro®
Trinipatch®
What key warnings do I need to know about before giving this drug to my child?
Sometimes drugs are not safe when your child takes them
Tracking tools
learn more
from School Specialty a KidsHealth Educational Partner
Partner with KidsHealth


Nitrolingual TL : Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD - Microsoft Internet Explorer provided
http://www.webmd.com/drugs/drug-3746-Nitrolingual+TL.aspx?drugid=3746&drugname=Nitrolingual+TL&source=1
Drugs and Medications Center
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Pill Identifier
Drugs & Medications A-Z
Drugs & Medical Conditions
Drug Basics & Safety
Latest Drug News
Drugs Information on Mobile
Find a Vitamin
Medication Evaluator
Common Drugs
Adderall
Celexa
Cipro
Cymbalta
Flexeril
Hydrocodone
Lexapro
Lisinopril
Medrol
Microzide
Mobic
Naproxen
Neurontin
Prednisone
Drugs & Medications - Nitrolingual TL
Nitrolingual TL
BRAND NAME(S): Nitrolingual
Review this Drug
3 User Reviews
USES
SIDE EFFECTS
PRECAUTIONS
INTERACTIONS
OVERDOSE
NITROLINGUAL TL USES
This medication is used before physical activities (such as exercise, sexual activity) to prevent chest pain (angina) in people with a certain heart condition (coronary artery disease). It may also be used to relieve chest pain in these people once it occurs.
Nitroglycerin belongs to a class of drugs known as nitrates. Angina occurs when the heart muscle is not getting enough blood. This drug works by relaxing and widening blood vessels so blood can flow more easily to the heart.
How to use Nitrolingual TL
Ask your doctor now for exact instructions on how to use your nitroglycerin and when to call for emergency medical help (911).
Read the Patient Information Leaflet available from your pharmacist. Consult your doctor or pharmacist if you have any questions.
Before using this medication for the first time, spray the pump into the air away from yourself, others, or open flame. This is known as priming the pump. The number of times you need to spray the pump to prime it depends on your brand. If you have not used this medication for 6 weeks or more, you will need to prime it again before use.
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Relapsing MS
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Giving Medicine to Children
HCG Diet Products Are Illegal
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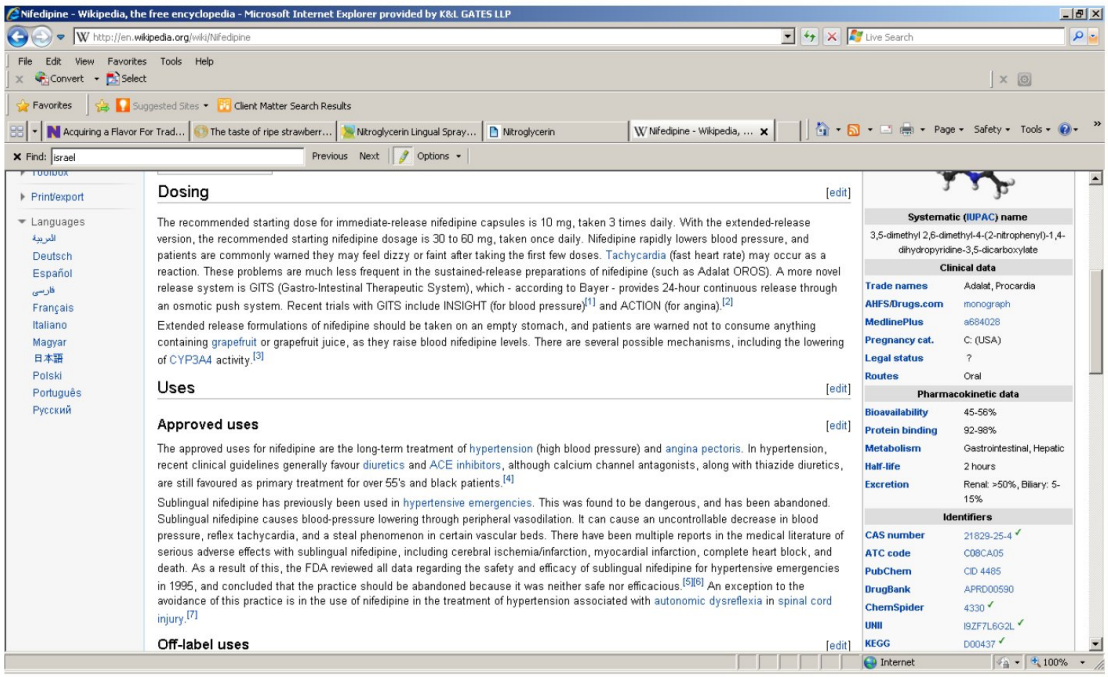
Nifedipine - Wikipedia, the free encyclopedia - Microsoft Internet Explorer provided by K&L GATES LLP
http://en.wikipedia.org/wiki/Nifedipine
Dosing
Uses
Approved uses
Off-label uses
Systematic (IUPAC) name
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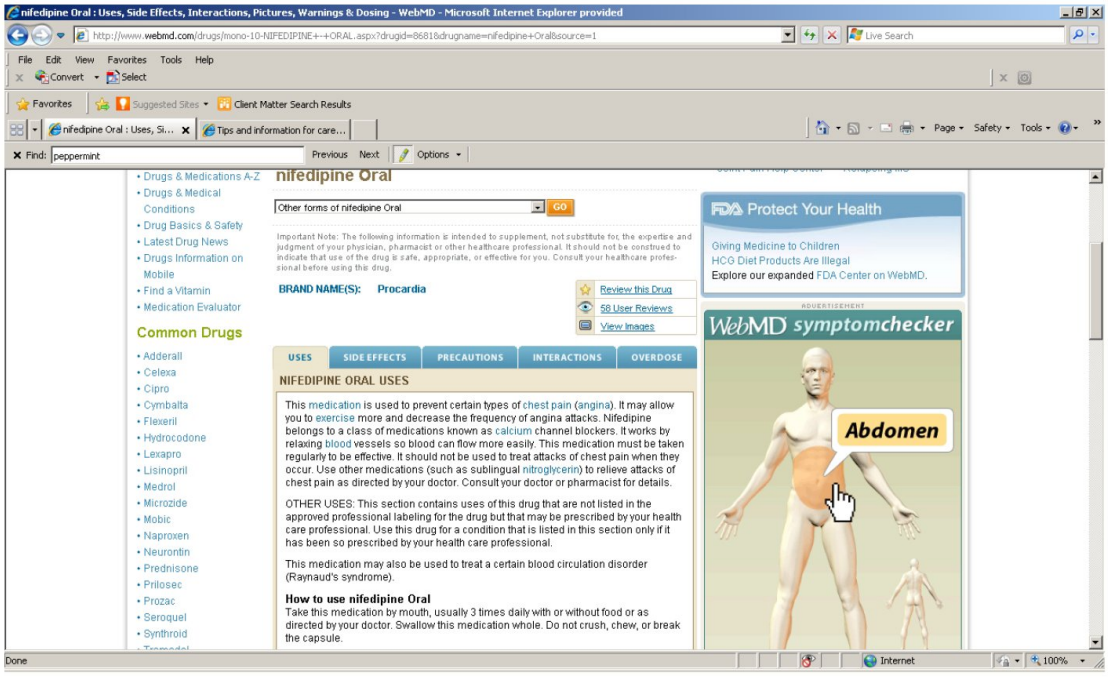
Clinical data
Pharmacokinetic data
Identifiers


nifedipine Oral : Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD - Microsoft Internet Explorer provided
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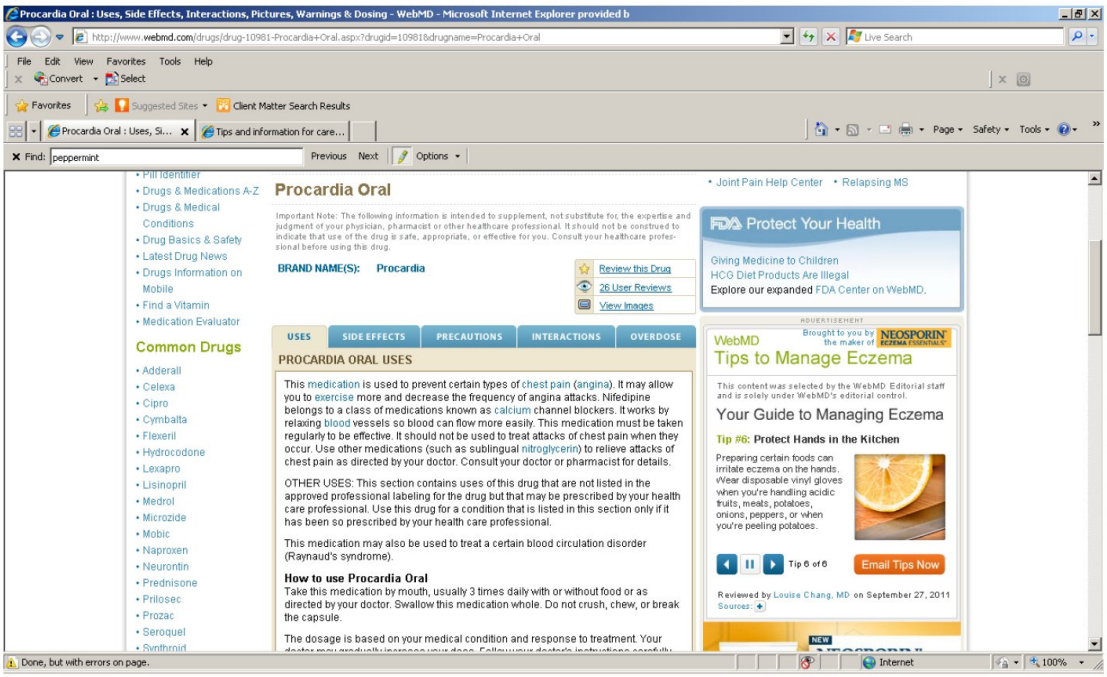
NIFEDIPINE ORAL USES
Common Drugs
FDA Protect Your Health
WebMD symptomchecker
Abdomen


Procardia Oral : Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD - Microsoft Internet Explorer provided b
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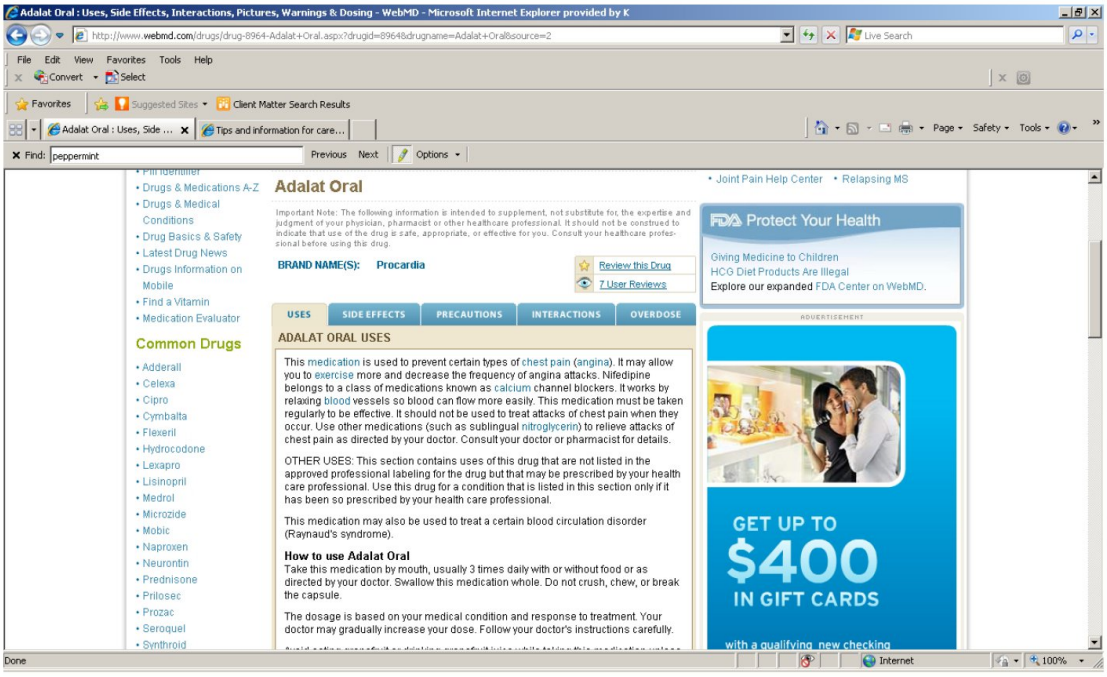
Procardia Oral
BRAND NAME(S): Procardia
USES
SIDE EFFECTS
PRECAUTIONS
INTERACTIONS
OVERDOSE
PROCARDIA ORAL USES
Common Drugs
Protect Your Health
Tips to Manage Eczema
Your Guide to Managing Eczema
Tip #6: Protect Hands in the Kitchen
Email Tips Now


Adalat Oral : Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD - Microsoft Internet Explorer provided by K
http://www.webmd.com/drugs/drug-8964-Adalat+Oral.aspx?drugid=8964&drugname=Adalat+Oral&source=2
Adalat Oral
BRAND NAME(S): Procardia
USES
SIDE EFFECTS
PRECAUTIONS
INTERACTIONS
OVERDOSE
ADALAT ORAL USES
Common Drugs
Protect Your Health
GET UP TO
$400
IN GIFT CARDS


A comparison of sublingual nifedipine versus ni... [DICP. 1989 Jul-Aug] - PubMed - NCBI - Microsoft Internet Explorer provided
http://www.ncbi.nlm.nih.gov/pubmed/2503945
File Edit View Favorites Tools Help
Convert Select
Favorites Suggested Sites Client Matter Search Results
A comparison of sublingu... Tips and information for care...
Find: peppermint Previous Next Options
NCBI Resources How To My NCBI Sign In
PubMed.gov US National Library of Medicine National Institutes of Health
PubMed Search
Limits Advanced Help
Display Settings: Abstract Send to:
Performing your original search, nitroglycerin vs nifedipine, in PubMed will retrieve 29 records.
DICP. 1989 Jul-Aug;23(7-8):562-4.
A comparison of sublingual nifedipine versus nitroglycerin in the treatment of acute angina pectoris.
Mooss AN, Mohiuddin SM, Hilleman DE, Sketch MH Sr.
Creighton University Cardiac Center, Omaha, NE 68131.
Abstract
The administration of nifedipine by the sublingual rather than the oral route has been suggested to provide a more rapid onset of effect. We compared the safety and efficacy of sl nifedipine to sl nitroglycerin in patients who developed anginal chest pain during diagnostic exercise stress testing. Consecutive patients undergoing diagnostic Bruce treadmill exercise who had not had a recent myocardial infarction or undergone coronary bypass graft surgery and who were not taking nitrates, beta-blockers, digoxin, or calcium antagonists were eligible. Seventy-eight patients meeting the inclusion/exclusion criteria consented to participate. Of these 78, 13 developed chest pain necessitating exercise cessation and were randomized to either nitroglycerin or nifedipine. Nitroglycerin was initially given to seven patients and nifedipine to six patients. Complete pain relief was observed in five of seven (71 percent) nitroglycerin patients at two minutes postdose. At four minutes postdose, the remaining two nitroglycerin patients were essentially pain-free. At two minutes postdose, no patient receiving nifedipine had complete pain resolution, and only one patient (17 percent) had partial (greater than 50 percent) pain relief. At four minutes postdose, four of the nifedipine patients were crossed over to nitroglycerin. At two minutes after the nitroglycerin dose, all four patients had total pain relief. The remaining two nifedipine patients had partial pain relief and were not crossed over to nitroglycerin. Subjective side effects and changes in heart rate and blood pressure were not significantly different between nitroglycerin and nifedipine.(ABSTRACT TRUNCATED AT 250 WORDS)
Related citations
Antianginal and anti-ischemic efficacy of nicorandil compa [J Cardiovasc Pharmacol. 1992]
Large dose sublingual nitroglycerin in acute myocardial infarction: relief c [Am J Cardiol. 1982]
Medical treatment of patients with severe exertional and rest angina: dou [Br Heart J. 1987]
Review NitroMist nitroglycerin spray for angina. [Med Lett Drugs Ther. 2011]
Review Nitroglycerin-induced hypotension, bradycardia, and asystole: rej [Clin Cardiol. 1990]
See reviews...
See all...
Related information
Related Citations
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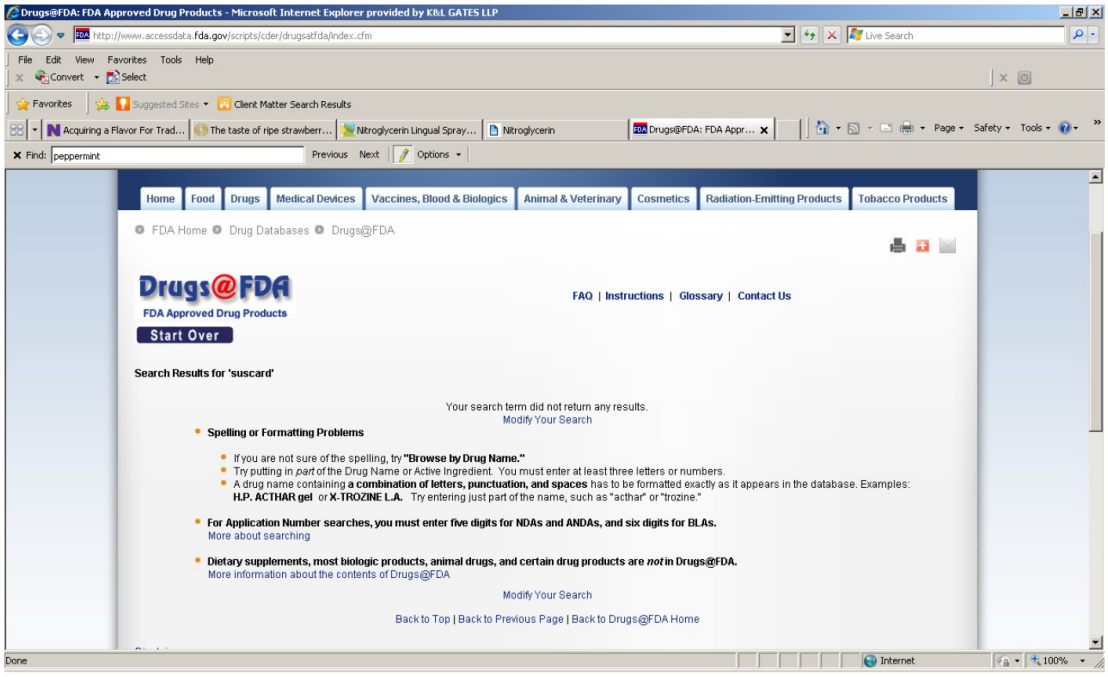
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http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
File Edit View Favorites Tools Help
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Acquiring a Flavor For Trad... The taste of ripe strawberr... Nitroglycerin Lingual Spray... Nitroglycerin Drugs@FDA: FDA Appr...
Find: peppermint Previous Next Options
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FDA Approved Drug Products
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Search Results for 'suscard'
Your search term did not return any results.
Modify Your Search
Spelling or Formatting Problems
If you are not sure of the spelling, try "Browse by Drug Name."
Try putting in part of the Drug Name or Active Ingredient. You must enter at least three letters or numbers.
A drug name containing a combination of letters, punctuation, and spaces has to be formatted exactly as it appears in the database. Examples: H.P. ACTHAR gel or X-TROZINE L.A. Try entering just part of the name, such as "acthar" or "trozine."
For Application Number searches, you must enter five digits for NDAs and ANDAs, and six digits for BLAs.
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Dietary supplements, most biologic products, animal drugs, and certain drug products are not in Drugs@FDA.
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EXHIBIT B

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

G. POHL-BOSKAMP GmbH & CO. KG, Plaintiff, v. AKRIMAX PHARMACEUTICALS, LLC, Defendant.	Civil Action No.: **JURY TRIAL DEMANDED**

COMPLAINT

Plaintiff G. Pohl-Boskamp GmbH & Co. KG, for its complaint against defendant Akrimax Pharmaceuticals, LLC, alleges as follows:

PARTIES

1. Plaintiff G. Pohl-Boskamp GmbH & Co. KG ("Pohl-Boskamp" or "Plaintiff") is a German corporation having a place of business in Hohenlockstedt, Germany.

2. Upon information and belief, defendant Akrimax Pharmaceuticals, LLC ("Akrimax" or "Defendant") is a Delaware limited liability company having a regular and established place of business at 11 Commerce Drive, Cranford, New Jersey.

JURISDICTION AND VENUE

3. This is a civil action for damages and injunctive relief brought pursuant to the Lanham Act, 15 U.S.C. § 1051, *et seq.*; the Copyright Act 17 U.S.C. § 101, *et seq.*; the Unfair and Deceptive Trade Practices Act, MASS. GEN. LAWS ch. 93A, §§ 1-11; and common law.

4. This Court has subject matter jurisdiction over this action pursuant to 15 U.S.C. § 1121 and 28 U.S.C. §§ 1331 and 1338(a) and (b) because Plaintiff Pohl-Boskamp's federal

claims arise under the Lanham Act, 15 U.S.C. § 1051, *et seq.* and the Copyright Act, 17 U.S.C. § 101 *et seq.* This Court has subject matter jurisdiction over Plaintiff's related state law and common law claims pursuant to 28 U.S.C. §§ 1338(b) and 1367.

5. Upon information and belief, this Court has personal jurisdiction over Defendant Akrimax because, among other reasons, on information and belief, it has sold or transported in Massachusetts goods and/or services that bear the accused trademarks and include the accused advertising and copied materials for use and sale in Massachusetts, Akrimax's tortious conduct has taken place and continues to take place in Massachusetts, and/or Akrimax regularly solicits business in Massachusetts.

6. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b) and (c) and § 1400 (a) in that, upon information and belief, Defendant Akrimax is subject to personal jurisdiction in the Commonwealth of Massachusetts and/or the wrongful acts committed by Defendant occurred in and are causing injury in the Commonwealth of Massachusetts.

FACTS COMMON TO ALL CLAIMS FOR RELIEF

Plaintiff's Nitrolingual® Pumpspray

7. Plaintiff Pohl-Boskamp is in the business of researching, developing and manufacturing pharmaceutical products and medical devices.

8. Pohl-Boskamp uses, and has used since at least as early as March 9, 1976 in the United States, the trademark Nitrolingual® in connection with pharmaceutical formulations of nitroglycerin. Pohl-Boskamp is the owner of the incontestable United States trademark registration number 1035175 for the mark NITROLINGUAL®. See Exhibit A.

9. Among these NITROLINGUAL® pharmaceutical products is the Nitrolingual® Pumpspray, a pumpspray bottle dispensing nitroglycerin and used to provide relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

10. The symptoms of angina pectoris include an uncomfortable pressure, fullness, squeezing, or pain in the center of the chest. Discomfort also may be felt in the neck, jaw, shoulder, back, or arm.

11. In the United States, one out of six people over age sixty-five develop coronary artery disease each year. According to the American Heart Association, almost nine million people in the United States suffer from angina pectoris.

12. Pohl-Boskamp's Nitrolingual® Pumpspray provides fast and effective relief dispensed through a convenient handheld pumpspray for those millions suffering from the pain and discomfort of angina pectoris.

13. Nitrolingual® Pumpspray was introduced to the United States market in or around 1976 and since then has enjoyed a significant share of the market for nitroglycerin pharmaceutical products.

14. Since its introduction, Pohl-Boskamp and its agents have spent tens of millions of dollars marketing its Nitrolingual® Pumpspray throughout the United States. Examples of Pohl-Boskamp's marketing materials for its Nitrolingual® Pumpspray are attached as Exhibit B. As a result of these efforts, the Nitrolingual® Pumpspray products have generated hundreds of millions of dollars in domestic sales.

15. Pohl-Boskamp has made and continues to make substantial investments to develop and promote the goodwill associated with its Nitrolingual® Pumpspray product.

Defendant's NitroMist® aerosol spray

16. Defendant Akrimax manufactures, distributes, and markets a recently-introduced competing prescription drug product, NitroMist®.

17. The NitroMist® product is an aerosol bottle dispensing nitroglycerin and, like Pohl-Boskamp's Nitrolingual® product, is intended to provide relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

18. Side by side photographs of Pohl-Boskamp's Nitrolingual® Pumpspray and Defendant's NitroMist® aerosol spray appear below:

Pohl-Boskamp's Nitrolingual® Pumpspray	**Defendant's NitroMist® product**
	

19. Despite some similarities, Defendant's NitroMist® product differs from Pohl-Boskamp's Nitrolingual® Pumpspray product in a number of ways, including the nitroglycerin formulation, the dosage form, the spray mechanisms, and the container-closure systems.

20. In its marketing and promotion of its NitroMist® product in United States commerce, Defendant has made numerous false and/or misleading statements relating to its

NitroMist® product and relating to Pohl-Boskamp's Nitrolingual® Pumpspray product and the Nitrolingual® brand.

21. Upon information and belief, consumers of Pohl-Boskamp's product were lost or diverted to Defendant.

Akrimax's False and/or Misleading Statements Regarding Defendant's Own Product

22. In its promotional materials for the NitroMist® product, Defendant has made false and/or misleading statements regarding the superiority and efficacy of its products.

23. Specifically, Defendant's promotional materials bear prominent statements touting the formulation of the Akrimax product with "soothing menthol," see Exhibit C at page 2, misleading consumers to believe that the menthol ingredient in Akrimax's NitroMist® product leads to increased effectiveness.

24. Furthermore, Defendant Akrimax claims that the menthol "enhances oral transmucosal absorption." See Exhibit C at page 2. Upon information and belief, Defendant has no clinical data supporting its enhanced absorption claim.

Akrimax's False and/or Misleading Statements Regarding Pohl-Boskamp's Nitrolingual® Pumpspray

25. Likewise, Defendant has made false and/or misleading statements regarding Pohl-Boskamp's Nitrolingual® Pumpspray.

26. Perhaps most troubling and damaging, Defendant's false and/or misleading claims state or imply that Pohl-Boskamp's Nitrolingual® Pumpspray fails to deliver a consistent dose in each spray and that doses from Pohl-Boskamp's Nitrolingual® Pumpspray may vary depending on pressure levels applied to the pump. See Exhibit C (at page 2) and Exhibit D (at pages 8 and 9). These untrue statements suggest to consumers that Pohl-Boskamp's Nitrolingual® Pumpspray is unsafe or dangerous to its users.

27. In fact, Pohl-Boskamp's unique pumpspray system ensures a consistently measured dose regardless of the pressure applied to the pump button.

28. Overall, the statements in Defendant's marketing and promotional materials unlawfully state or imply that NitroMist® is more effective than Nitrolingual® Pumpspray. See Exhibits C, D, and E. These false and misleading Akrimax statements and claims include:

> Nitroglycerin lingual spray formulations are currently available in two distinct device configurations that differ in design and use (Table 4). NitroMist® (nitroglycerin lingual aerosol) is fully sealed at manufacture, with inert nonchlorofluorocarbon (CFC) propellant added. The closed system represents an important advance, ensuring consistent delivery of nitroglycerin with a 36-month shelf life. Nitrolingual® Pumpspray (nitroglycerin lingual spray) is packaged in a glass bottle that is not a closed system. The shelf life of this product is 24 months.
>
> Administration of nitroglycerin lingual spray also differs between these devices. NitroMist uses a novel, patented valve technology designed to deliver a consistent dose (400 mcg) at each actuation. Adequate pressure must be applied to activate the metered valve. To administer, the actuator button is pressed firmly with the forefinger, delivering one or two sprays. The metered valve forces the product to the buccal area where absorption occurs. Nitrolingual Pumpspray (nitroglycerin lingual spray) is a metered pump spray. For administration, the patient is directed to press the spray button firmly with the forefinger, delivering one or two sprays. As with NitroMist, adequate pressure must be applied to activate the metered valve.

(Exhibit D at p. 8).

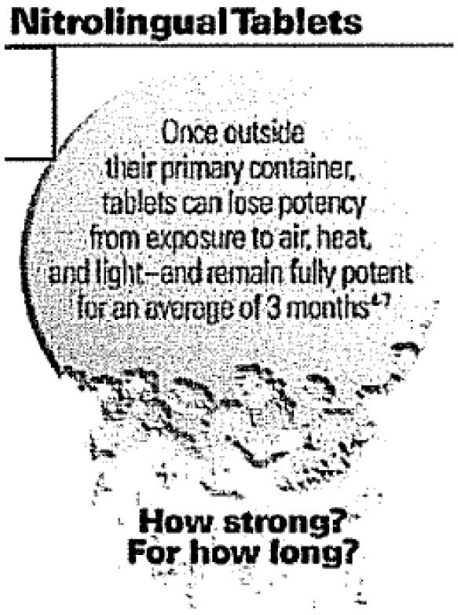
Use of a table (shown below and in Exhibit C) that specifically compares NitroMist® Aerosol to Nitrolingual® Pumpspray, while inaccurately describing or misrepresenting information regarding spray, spray device, inactive ingredients and shelf life.

NitroMist Aerosol	Nitrolingual Pumpspray
• Propellant-driven ultrafine mist via metered dose ensures consistent delivery*	• Volume sprayed depends on pressure applied
• Adequate pressure must be applied to activate metered valve	• Adequate pressure must be applied to activate metered valve
• Contains soothing menthol, which also enhances oral transmucosal absorption[3,4]	• Contains 20% ethanol[5]
• 36-month shelf life	• 24-month shelf life

(Exhibit C)

False Statements Regarding the Nitrolingual® brand and Misuse of Pohl-Boskamp's Registered Trademark

29. Defendant also has misused Pohl-Boskamp's registered NITROLINGUAL® mark with reference to "Nitrolingual tablets" (shown below) despite the fact that Pohl-Boskamp does not offer a nitroglycerin tablet. See Exhibit C at page 2.



30. Akrimax's intent to trade on Pohl-Boskamp's goodwill and trademark rights is further shown by Akrimax's unlawful registration and use of the following domain names, which wholly incorporate or are substantially similar to Pohl-Boskamp's registered trademark, to divert internet users searching for Pohl-Boskamp's Nitrolingual® product:

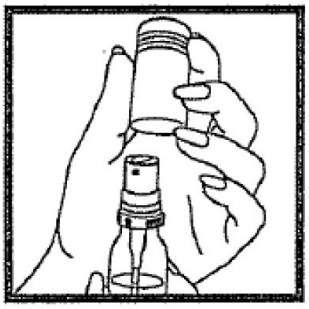
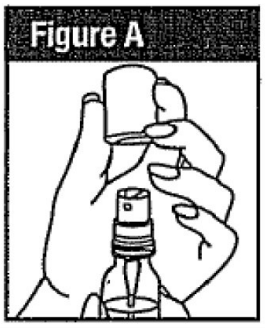
- nitrolingualspray.com
- nitrolingual.net
- nitrolingualspray.net

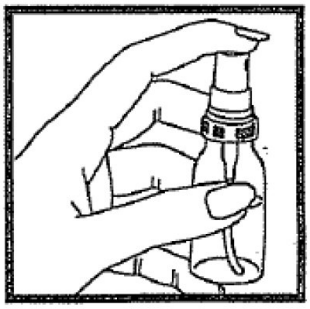
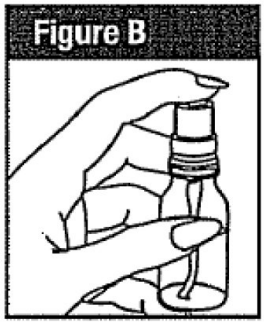
Defendant's Blatant Copying of Pohl-Boskamp's Product Inserts and Illustrations

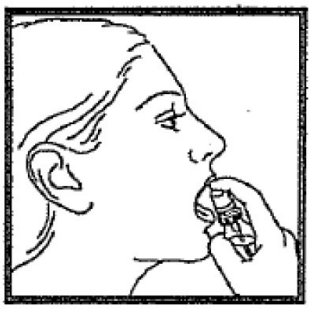
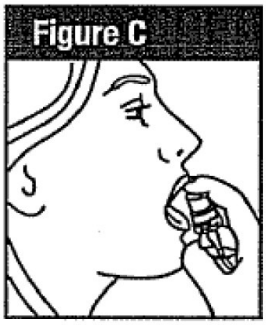
31. Not only has Defendant misused Pohl-Boskamp's trademark and made false and misleading statements regarding Pohl-Boskamp's Nitrolingual® Pumpspray, Defendant has

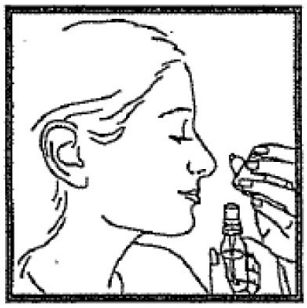
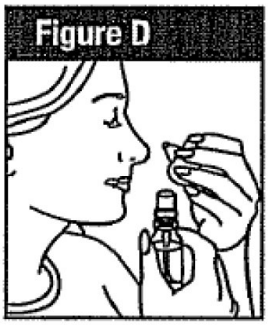
blatantly copied without authorization copyrighted illustrations depicting Pohl-Boskamp's pumpspray product and has used these drawings to promote to consumers Defendant's NitroMist® aerosol product. See Exhibit D (at pages 20 and 21) and Exhibit F.

32. A side by side comparison of Pohl-Boskamp's copyrighted illustrations and Defendant's infringing copies appears below:

Pohl-Boskamp's Copyrighted Work	Defendant's Infringing Copy
	

Pohl-Boskamp's Copyrighted Work	Defendant's Infringing Copy
	

Pohl-Boskamp's Copyrighted Work	Defendant's Infringing Copy
	

Pohl-Boskamp's Copyrighted Work	Defendant's Infringing Copy
	

33. Indeed, Defendant's product insert for the NitroMist® aerosol product uses text substantially similar to that included in Pohl-Boskamp's product insert for Nitrolingual® Pumpspray. Compare Exhibit F with Exhibit G.

34. As a result of Defendant's actions as set forth above, Pohl-Boskamp has been damaged and irreparably harmed.

35. Unless enjoined by this Court, Defendant's actions will continue and will result in further irreparable harm to Pohl-Boskamp.

COUNT I: FEDERAL FALSE ADVERTISING AND UNFAIR COMPETITION UNDER § 43(A) OF THE LANHAM ACT, 15 U.S.C. §1125(A)

36. Pohl-Boskamp repeats and realleges each and every allegation contained in paragraphs 1-35 of the Complaint with the same force and effect as if set forth in this Count.

37. Defendant created and distributed marketing materials that include the various false and/or misleading statements, including those set forth above and included in Exhibits C, D and E.

38. Defendant's statements explicitly and implicitly convey, among other things, that Nitrolingual® Pumpspray does not deliver a consistent dose in each spray, that Nitrolingual® Pumpspray does not deliver a full 400 mcg/spray, that NitroMist® is superior to Nitrolingual Pumpspray, when that is not the case.

39. Such explicitly and implicitly false statements have caused and will continue to cause Pohl-Boskamp significant harm to its goodwill and to its sales.

40. For those reasons, Defendant's statements constitute false or misleading representations in connection with commercial advertising and promotion in willful and intentional violation of § 43(a) of the Lanham Trademark Act, 15 U.S.C. § 1125(a).

41. Pohl-Boskamp has been damaged and will continue to be damaged by Defendant's acts unless Defendant is preliminarily and thereafter permanently enjoyed by this Court.

42. Pohl-Boskamp is without an adequate remedy at law.

COUNT II: FEDERAL TRADEMARK INFRINGEMENT UNDER 15 U.S.C. § 1114

43. Pohl-Boskamp repeats and realleges each and every allegation contained in paragraphs 1-42 of the Complaint with the same force and effect as if set forth in this Count.

44. Pohl-Boskamp's NITROLINGUAL® trademark is inherently distinctive and/or have obtained distinctiveness. The NITROLINGUAL® trademark is incontestable.

45. Defendant's use of Pohl-Boskamp's NITROLINGUAL® mark to describe nitroglycerin "tablets" may cause consumers to be confused or deceived into believing that the nitroglycerin tablets are products of, or are sponsored or endorsed by Pohl-Boskamp and/or otherwise constitute violations of Section 43(a) of the Lanham Act. Likewise, Defendant's registration and/or use of domain names wholly incorporating Pohl-Boskamp's NITROLINGUAL® mark violate Section 43(a) of the Lanham Act.

46. Pohl-Boskamp has been damaged and will continue to be damaged by Defendant's acts unless Defendant is preliminarily and thereafter permanently enjoyed by this Court.

47. Pohl-Boskamp is without an adequate remedy at law.

COUNT III: STATE FALSE ADVERTISING AND UNFAIR COMPETITION LAW UNDER MASS. GEN. LAWS ch. 93A, §§ 1-11

48. Pohl-Boskamp repeats and realleges each and every allegation contained in paragraphs 1-47 of the Complaint with the same force and effect as if set forth in this Count.

49. Defendant's acts within Massachusetts as described in this complaint constitute unfair or deceptive acts or practices in Massachusetts within the meaning of MASS. GEN. LAWS ch. 93A §§ 2 and 11.

50. Defendant's violations of MASS. GEN. LAWS ch. 93A §§ 2 and 11 caused Pohl-Boskamp substantial damages in Massachusetts in an amount to be determined at trial.

51. Pohl-Boskamp has been damaged and will continue to be damaged by Defendant's acts unless Defendant is preliminarily and thereafter permanently enjoyed by this Court.

52. Pohl-Boskamp is without an adequate remedy at law.

COUNT IV: FEDERAL COPYRIGHT INFRINGEMENT

53. Pohl-Boskamp repeats and realleges each and every allegation contained in paragraphs 1-52 of the Complaint with the same force and effect as if set forth in this Count.

54. Pohl-Boskamp's illustrations and product insert text constitute copyrightable works protected under Title 17 of the United States Code.

55. Pohl-Boskamp is the sole owner of all right, title, and interest in and to the copyrights in the text included in its product insert and to drawings depicting (a) a pumpspray bottle with its cap being removed by a hand; (b) a hand holding a pumpspray bottle with the index finger positioned to depress the bottle's pump button; (c) the head of a female shown in profile view, with a pumpspray bottle held to the mouth as the index finger depresses the bottle's pump button; (d) the head and shoulders of a female shown in profile view, holding a pumpspray bottle and replacing its cap.

56. Upon information and belief, Defendant had access to the copyrighted works.

57. Without Pohl-Boskamp's permission, Defendant copied copyrighted subject matter of Pohl-Boskamp's illustrations and product insert text.

58. By reproducing, displaying, distributing and/or making derivative works of the copyrighted works without Pohl-Boskamp's permission, Defendant's actions constitute infringement of Pohl-Boskamp's exclusive rights under the Copyright Act, 17 U.S.C. §§ 106 and 501.

59. Upon information and belief, Defendant's actions were a knowing, intentional and deliberate violation of Pohl-Boskamp's copyrights, and its infringement was committed willfully within the meaning of 17 U.S.C. § 504.

60. Pohl-Boskamp is the owner of United States copyright applications 1-559667731, 1-559667753, 1-559569421, 1-559667609, 1-559667785, filed on an expedited basis on February 4, 2011. Copies of Pohl-Boskamp's copyright applications and the drawings submitted to the United States Copyright Office are attached as composite Exhibit H.

61. In addition, Pohl-Boskamp is a corporation organized under the laws of Germany, a signatory to the Berne Convention, and thus exempted from the preregistration and registration requirements of 17 U.S.C. § 411(a).

62. Pohl-Boskamp has been damaged and will continue to be damaged by Defendant's acts unless Defendant is preliminarily and thereafter permanently enjoyed by this Court.

63. Pohl-Boskamp is without an adequate remedy at law.

WHEREFORE, Plaintiff respectfully demands judgment against Defendant Akrimax as follows:

A. Preliminarily and permanently enjoining Defendant Akrimax, including its officers, directors, employees, agents, servants, successors and assigns, as well as all those in active concert and participation with it, from making further false or misleading statements about or relating to Defendant's NitroMist® product or any of Pohl-Boskamp's products.

B. Ordering that all false or misleading and/or infringing articles in Defendant Akrimax's possession, including but not limited to products, labels, signs, prints, packaging and advertisements be delivered to an officer of the Court to be destroyed;

C. Ordering that Defendant Akrimax recall from all customers, distributors, and agents all false or misleading and/or infringing articles, including but not limited to products, labels, signs, prints, packaging and advertisements, and deliver such articles to an officer of the Court to be destroyed;

D. Ordering that Defendant Akrimax prepare and distribute corrective advertising sufficient to remedy the harm caused by Akrimax's false and/or misleading statements;

E. Assessing against Defendant Akrimax and awarding to Pohl-Boskamp damages, including without limitation actual damages and Defendant Akrimax's profits, and conducting an accounting to determine such damages;

F. Increasing damages by three times the actual amount found;

G. Awarding Pohl-Boskamp the costs of this action and reasonable attorneys' fees; and

H. Granting to Pohl-Boskamp such other and further relief as this Court may deem just and proper.

JURY DEMAND

Plaintiff Pohl-Boskamp hereby demands trial by jury as to all issues in this action triable of right by a jury.

Dated: February 7, 2011

Respectfully submitted,

/s/ Sara Y. Beccia

John J. Cotter (BBO # 554524)
Phi Lan M.Tinsley (BBO # 656815)
Sara Yevics Beccia (BBO # 667277)
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PhiLan.Tinsley@klgates.com
Sara.Beccia@klgates.com

Counsel for Plaintiff G. Pohl-Boskamp GmbH & Co. KG

CERTIFICATE OF SERVICE

I hereby certify that a true copy of the above document was filed with this Court conventionally on February 7, 2011 and will be served with the Complaint in this Action as indicated in the Summons.

/s/ Sara Y. Beccia
Sara Yevics Beccia (BBO # 667277)

EXHIBIT A

Int. Cl.: 5

Prior U.S. Cl.: 18

United States Patent Office

Reg. No. 1,035,175

Registered Mar. 9, 1976

TRADEMARK

Principal Register

NITROLINGUAL

Arthur Boskamp, doing business as G. Pohl-Boskamp
2214 Hohenlochstedt
Holstein, West Germany

For: MEDICINES—NAMELY, PHARMACEUTI-CAL FORMULATIONS OF NITROGLYCERIN—it CLASS 5 (U.S. CL. 18).

Owner of German Reg. No. 609,883, dated Dec. 3 1949.

Ser. No. 62,058, filed Sept. 4, 1975.

R. H. NEILSON, Examiner

Int. Cl.: 5

Prior U.S. Cl.: 18

United States Patent and Trademark Office

10 Year Renewal

Reg. No. 1,035,175

Registered Mar. 9, 1976

Renewal Term Begins Mar. 9, 1996

TRADEMARK
PRINCIPAL REGISTER

NITROLINGUAL

G. POHL-BOSKAMP GMBH & CO. (FED REP GERMANY CORPORATION)
KIELER STRASSE 11
25551 HOHENLOCKSTEDT, FED REP GERMANY, BY CHANGE OF NAME FROM BOSKAMP, ARTHUR (FED REP GERMANY CITIZEN), DBA G. POHL-BOSKAMP, HOLSTEIN, FED REP GERMANY

OWNER OF FED REP GERMANY REG. NO. 609883, DATED 12-3-1949.

FOR: MEDICINES—NAMELY, PHARMACEUTICAL FORMULATIONS OF NITROGLYCERIN, IN CLASS 5 (U.S. CL. 18).

SER. NO. 73-062,058, FILED 9-4-1975.

In testimony whereof I have hereunto set my hand and caused the seal of The Patent and Trademark Office to be affixed on Aug. 20, 1996.

COMMISSIONER OF PATENTS AND TRADEMARKS

EXHIBIT B


Nitrolingual Pumpspray is a stable, potent and reliable choice for rapid angina relief.
Stability & Potency
• Proven stability for at least two years from the date of manufacture
• No concerns regarding loss of potency due to light, moisture or handling
Rapid Pain Relief
• In one study, 69% of patients reported pain relief within 60 seconds vs. 38% of patients who used tablets (n=352)[6]
• In another study, 62% of patients receiving the spray gained relief in less than one minute vs. 36% of patients receiving tablets (n=797)[7]
Ease of Use
• Consistent dosing with each metered spray
• Eliminates the need to fumble with hard-to-open prescription bottles and small tablets
• Pain relief not affected by dry mouth[8]
• 2 convenient bottle sizes:
- 4.9g (60 metered sprays)
- 12g (200 metered sprays)
Actual Size
Indications and Usage Nitrolingual® Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.
Important Safety Information Nitrolingual Pumpspray should not be used while taking phosphodiesterase inhibitors which are used for the treatment of erectile dysfunction. Nitrolingual Pumpspray should be used with caution if patients have low systolic blood pressure, are undergoing diuretic therapy, or show hypersensitivity to this and other nitrates or nitrites. Headache is the most commonly reported side effect with nitroglycerin. Patients may also experience episodes of dizziness, weakness, and other related side effects.
Prescribe Nitrolingual® Pumpspray and give your patients
angina relief they can count on
Generic Now Available!
Patients pay $0 co-pay**
Actual Size
Stability & Potency
Rapid Pain Relief
Ease of Use
For Presentation Purposes Only. Not to be Left With Physician.
Nitrolingual Pumpspray
(nitroglycerin lingual spray)
0.4 mg nitroglycerin per spray
Reliable angina relief –
Nitrolingual® Pumpspray
(nitroglycerin lingual spray)
Generic Now Available!
Stability & Potency
Rapid Pain Relief
Ease of Use
Nitrolingual Pumpspray is a stable, potent and reliable choice for rapid angina relief.

Stability & Potency

Nitroglycerin is inherently unstable. For this reason:

- Nitroglycerin is potentially less effective due to improper storage, light, moisture, or handling.[1,2]
- According to the P.I. for Nitrostat: "Nitroglycerin should be kept in the original glass container, tightly capped."
- Studies show patients commonly fail to follow these guidelines, potentially compromising effectiveness.[3,4]

In addition, more than one-third of CHD patients carry tablets that are older than 6 months.[5]

Nitrolingual Pumpspray has:

- **Proven stability for at least two years** from the date of manufacture
- **No concerns regarding loss of potency** due to light, moisture or handling*

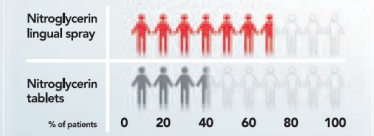
*Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [See USP Controlled Room Temperature].

www.nitrolingual.com

Rapid Pain Relief

More patients received pain relief within 60 seconds v. tablets

- In a study of 352 patients, 69% reported pain relief within 60 seconds v. 38% of patients who used tablets[6]



Results of an 8-week randomized study comparing the efficacy and tolerability of nitroglycerin spray vs tablets in patients with a clinical history of angina pectoris.

In another study, 62% of patients receiving the spray gained relief in less than one minute vs. 36% of patients receiving tablets (n=797)[7]

www.nitrolingual.com

Ease of Use

- Consistent dosing with each metered spray
- Eliminates the need to fumble with hard-to-open prescription bottles and small tablets
- Pain relief not affected by dry mouth[8]

Nitrolingual Pumpspray is available in two convenient bottle sizes: A 60 metered spray bottle and a 200 metered spray bottle

Actual Size

Indications and Usage Nitrolingual® Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

Important Safety Information Nitrolingual Pumpspray should not be used while taking phosphodiesterase inhibitors which are used for the treatment of erectile dysfunction. Nitrolingual Pumpspray should be used with caution if patients have low systolic blood pressure, are undergoing diuretic therapy, or show hypersensitivity to this and other nitrates or nitrites. Headache is the most commonly reported side effect with nitroglycerin. Patients may also experience episodes of dizziness, weakness, and other related side effects.

Nitrolingual® Pumpspray
(nitroglycerin lingual spray)
0.4 mg nitroglycerin per spray

www.nitrolingual.com

EXHIBIT C

NEW

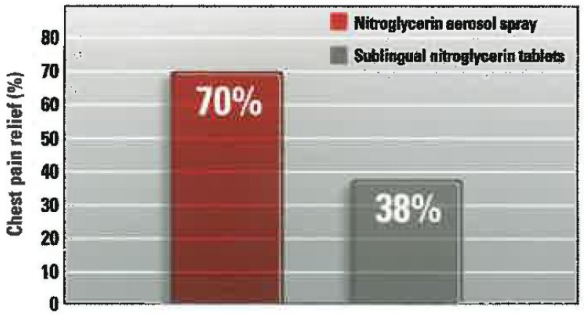
NITROMIST®

Nitroglycerin Lingual Aerosol • 400 mcg/spray

In a study using nitroglycerin aerosol spray, most angina patients experienced

Relief in less than 60 seconds

Patients experiencing chest pain relief in less than 60 seconds (n=352)[1]

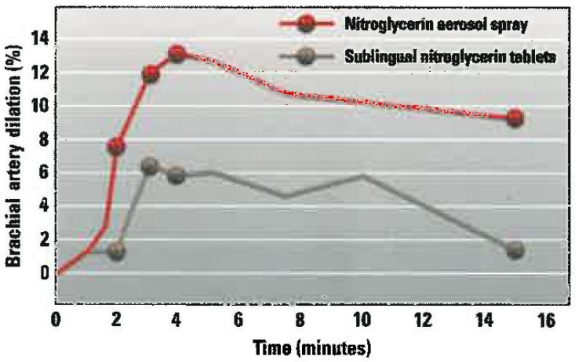


- Significantly faster than sublingual tablets[1]
- Fewer, less severe headaches in patients treated with aerosol spray[1]

In another study using a nitroglycerin aerosol spray, vasodilation was

Faster, greater, and longer

Effect of 0.4 mg nitroglycerin aerosol spray and sublingual tablets on brachial artery vasodilation in normal subjects (n=20)



- Vasodilation was faster, greater, and longer in duration than sublingual tablets[2]

Safety Considerations

As with all nitroglycerin products, the most common adverse reactions are headache, flushing, hypotension, and syncope. NitroMist is contraindicated in patients using a phosphodiesterase inhibitor (for erectile dysfunction) and in patients with severe anemia. Excessive use may lead to tolerance. Please see accompanying full Prescribing Information.

EVERY SECOND COUNTS

AKRIMAX PHARMACEUTICALS

INTRODUCING

NitroMist®

Nitroglycerin Lingual Aerosol • 400 mcg/spray

Patients get the same dose every time

NitroMist Aerosol	Nitrolingual Pumpspray	Nitrolingual Tablets
• Propellant-driven ultrafine mist via metered dose ensures consistent delivery*	• Volume sprayed depends on pressure applied	Once outside their primary container, tablets can lose potency from exposure to air, heat, and light—and remain fully potent for an average of 3 months[6,7]
• Adequate pressure must be applied to activate metered valve	• Adequate pressure must be applied to activate metered valve	
• Contains soothing menthol, which also enhances oral transmucosal absorption[3,4]	• Contains 20% ethanol[5]	
• 36-month shelf life	• 24-month shelf life	

*Delivery technology does not necessarily affect clinical outcomes.

How strong?
For how long?

Safety Considerations

Unit must be primed by pressing actuator button 10 times before initial use. If product is not used for more than 6 weeks, it can be adequately reprimed with 2 sprays. During use the patient should rest, ideally in the sitting position. The dose should be sprayed into the mouth or under the tongue by pressing the actuator button firmly and the mouth should be closed immediately after each dose. The spray should not be inhaled.
Please see accompanying full Prescribing Information.

References: 1. Vandenburg MJ, Griffiths GK, Brandman S. Sublingual nitroglycerin or spray in the treatment of angina. *Br J Clin Pract.* 1986;40(12):524-527. **2.** Ducharme A, Dupuis J, McNicoll S, et al. Comparison of nitroglycerin lingual spray and sublingual tablet on time of onset and duration of brachial artery vasodilation in normal subjects. *Am J Cardiol.* 1999;84(8):952-954. **3.** Shojaei AH, Chang RK, Guo X, et al. Systemic drug delivery via the buccal mucosal route. *Pharm Tech.* 2001; www.pharmaportal.com. Accessed 10/26/2010. **4.** Nitin J, Pallavi M, Kumar SK. Buccoadhesive drug delivery--a potential route of drug administration. *Int J Pharm Biol Arch.* 2010;1(1):11-23. **5.** Nitrolingual Pumpspray Prescribing Information. Sciele Pharma Inc., a Shionogi Company; 2008. **6.** O'Hanrahan M, McGarry K, Keily JG, et al. Diminished activity of glyceryl trinitrate. *Br Med J.* 1982;284(6323):1183-1184. **7.** Davis's Drug Guide.com. http://www.drugguide.com/ddo/ub/view/Davis-Drug-Guide/51548/all/nitroglycerin?q=nitroglycerin. Published 2010. Accessed June 21, 2010. **8.** Tallett ER. Stability of glyceryl trinitrate tablets (letter). *Br Med J.* 1982;284:1403. **9.** Hilleman DE, Banakar UV. Issues in contemporary drug delivery. Part VI: Advanced cardiac drug formulations. *J Pharm Technol.* 1992;8(5):203-211.

EXHIBIT D

NitroMist®
Product Dossier

NITROMIST
Nitroglycerin Lingual Aerosol • 400 mcg/spray

Table of Contents

Introduction

As the leading cause of death in the United States, ischemic heart disease is a major public health problem. In approximately half of patients, the disease process manifests initially as chronic stable angina pectoris (or simply angina), a type of chest pain or discomfort characterized by pressure, fullness, squeezing, or pain in the center of the chest. Anginal pain may radiate to the neck, jaw, shoulder, back, or arm and is typically aggravated by exertion or emotional stress. Current data suggest that more than 10 million Americans suffer from angina.

Causes and Classification of Angina

Broadly speaking, angina is caused by an imbalance between oxygen supply and demand in the myocardial tissue, resulting in ischemia, and, subsequently, chest pain. Four physiologic causes of angina have been identified, of which atherosclerotic heart disease is by far the most common. Atherosclerosis is an ongoing process of deposition of fatty substances, cholesterol, cellular waste products, calcium, and other substances leading to the buildup of plaque in the endothelial lining of large- and medium-sized coronary arteries, ultimately causing reduced blood flow and ischemia. Less common causes of angina include valvular heart disease, hypertrophic cardiomyopathy, and uncontrolled hypertension, which is defined as systolic and diastolic blood pressure ≥140 mm Hg and ≥90 mm Hg, respectively.

Three Classes of Angina are Recognized Clinically:

- Stable angina, the most common subtype, is characterized by predictable episodes of chest pain that occur with exertion or during mental or emotional stress
- Unstable angina is differentiated by its unpredictable nature. Pain experienced during an episode of unstable angina may be more severe than the pain of stable angina. It is associated with ischemia but not myocardial necrosis, often occurring with atherosclerotic plaque fissure or rupture with thrombus formation, but without complete occlusion of the vessel lumen
- Prinzmetal, or variant, angina is a variant form of unstable angina that results from coronary artery spasm. This pain occurs at rest, typically overnight, and is not associated with identifiable triggers or a predictable pattern

Clinical Consequences of Angina

One of the most serious clinical consequences of angina is a significantly increased risk for acute coronary syndrome (ACS), particularly myocardial infarction (MI). Indeed, the term acute coronary syndrome is increasingly used to describe patients who present to the healthcare system with either acute MI or unstable angina (UA), since these two entities share common pathophysiologic origins and are difficult to distinguish without a laboratory examination. Approximately 18% of MIs are preceded by longstanding angina pectoris.

Recent estimates of the prevalence of conditions associated with coronary heart disease (CHD) illustrate the large burden of disease including hospitalization and mortality associated with UA and MI (Table 1). According to estimates by the American Heart Association, more than 81 million Americans suffer from cardiovascular disease of one or more types. Of these, more than 17 million have coronary artery disease (CAD) and 9.8 million have angina pectoris. The most common heart-related reasons listed for hospital admission (in order of frequency) are congestive heart failure, chest pain, hardening of the arteries, MI, and irregular heart beat. In addition, it is estimated that more than half a million Americans (320,000 men and 180,000 women) 45 years of age and older will suffer from stable angina in 2010. Of note, the age-adjusted prevalence of angina is higher among some populations of women (eg, non-Hispanic black and Mexican-American women).

Table 1. US Burden of Disease: CHD, UA, and MI*

		Prevalence	Hospitalizations	Deaths
	CHD (all)	17,600,000	1,760,000	425,400
ACS	Angina pectoris (unstable)	10,200,000	537,000†	NS
	MI	8,500,000	810,000†	141,500

*Data from 2006. †An additional 18,000 discharges were coded as both unstable angina and myocardial infarction. NS=not stated.

The Role of Sublingual Nitroglycerin in Managing Angina

Mechanism of Action

The vasodilating effects of nitroglycerin, while not completely understood at the molecular level, have been recognized for many years. Nitroglycerin and other nitrates were shown to improve myocardial blood flow primarily through the relaxation of vascular smooth muscle, resulting in vasodilation of both arterial and venous beds. Increased blood flow leads to both increased myocardial oxygen supply and decreased oxygen demand, and reduces the pain associated with oxygen imbalance. Nitroglycerin promotes the dilation of large coronary arteries and increases collateral blood flow causing redistribution of coronary blood flow to ischemic regions.

In vascular smooth muscle and endothelial cells, nitroglycerin undergoes bioconversion into the free radical nitric oxide (NO), which in turn activates the enzyme guanylate cyclase. The precise mechanism by which nitroglycerin activates guanylate cyclase is not fully known. Increased enzymatic activity raises levels of cyclic guanosine monophosphate (cGMP), an intracellular second messenger that activates several protein kinases. Phosphorylation of multiple target proteins by these kinases regulates intracellular calcium mobilization, ultimately leading to vasodilation.

Place in Therapy of Nitroglycerin

Chest pain that is characteristic of angina may be the result of potentially life-threatening conditions, including ACS. Because of its rapid time to onset of pharmacodynamic effect (30 seconds to a few minutes), nitroglycerin is an important component in the triage and initial management of patients experiencing angina. Pain relief upon nitroglycerin administration is useful for distinguishing angina from other causes of chest pain and is of immediate therapeutic benefit. However, contrary to earlier beliefs about its diagnostic value, the response to nitroglycerin (ie, relief of anginal pain) has been shown in the emergency department (ED) setting to have low sensitivity and specificity for identifying those patients who have CAD.

Use in the Out-of-Hospital Setting

Guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) for the management of chronic stable angina recommend self-administration of nitroglycerin for patients with a history of chronic stable angina who have an existing prescription for the drug. For these patients (ie, who have received prior counseling), nitroglycerin is useful to manage acute episodes of chest pain. Either lingual spray or sublingual tablets can be used:

- For the immediate relief of angina occurring during exertion or at rest
- For prophylaxis to avoid episodes of ischemia and pain, taken several minutes prior to planned exertion or exercise

Patients with chronic stable angina do not generally need emergency medical services (EMS), usually accessed by dialing 9-1-1. However, it is important for patients, family members, and caregivers of those who self-administer nitroglycerin to have an action plan, including when to contact the healthcare system. Patients should be instructed to promptly administer nitroglycerin and told how to access EMS in their community. They should know the location of the nearest hospital that offers 24-hour emergency cardiovascular care. If chest discomfort is unimproved or worsens 5 minutes after using nitroglycerin lingual spray or taking one nitroglycerin sublingual tablet, ACC/AHA guidelines recommend activating the EMS system rather than calling a physician or driving to the hospital.

Use by EMS Staff

Nitroglycerin is an important component of the standard of care for managing cardiac-related chest pain in the prehospital setting. The ACC/AHA has published specific guidelines for its use by EMS staff in patients with suspected UA or ACS (Table 2). These actions are extremely time sensitive. For patients with chest pain that is suggestive of ischemia (ie, angina) and who are hemodynamically stable, EMS staff should administer nitroglycerin, as needed, for symptomatic relief. Up to 3 tablets (or sprays) are given for ongoing symptoms at intervals of 3 to 5 minutes. In the out-of-hospital setting, the use of nitroglycerin by EMS staff is largely directed by medical control contacts.

Table 2. ACC/AHA Guidelines on the Use of Nitroglycerin by EMS Staff

ACS (chest pain suggestive of ischemia) • Monitor and support ABCs • Be prepared to administer CPR and defibrillation • Administer as needed: oxygen, aspirin, sublingual nitroglycerin, morphine • Obtain 12-lead ECG		**STEMI** (ST-elevation myocardial infarction) • Notify hospital with transmission/interpretation of ECG • Begin fibrinolytic checklist **Unstable Angina or Non–ST-Elevation MI** (No ST elevation on ECG) • Notify hospital with transmission/interpretation of ECG

ABCs=airway, breathing, circulation; CPR=cardiopulmonary resuscitation; ECG=electrocardiogram.

Use by Hospital Staff in Acute Care Settings

Nitroglycerin spray or tablets continue to have utility after admission to the ED in the case of episodic and acute angina. Here, ECG findings and cardiac biochemical markers are used to confirm the patient's risk stratification into 1 of 3 categories: STEMI (ST-elevated myocardial infarction), high-risk, unstable angina/non–ST-elevation MI, or low-risk/inconclusive. Long-acting intravenous or oral nitrates are indicated in the first 24 to 48 hours after admission for patients with recurrent ischemia in acute care settings (eg, intensive or cardiac care units and in-hospital "crash-carts").

Contraindications to Nitroglycerin Use

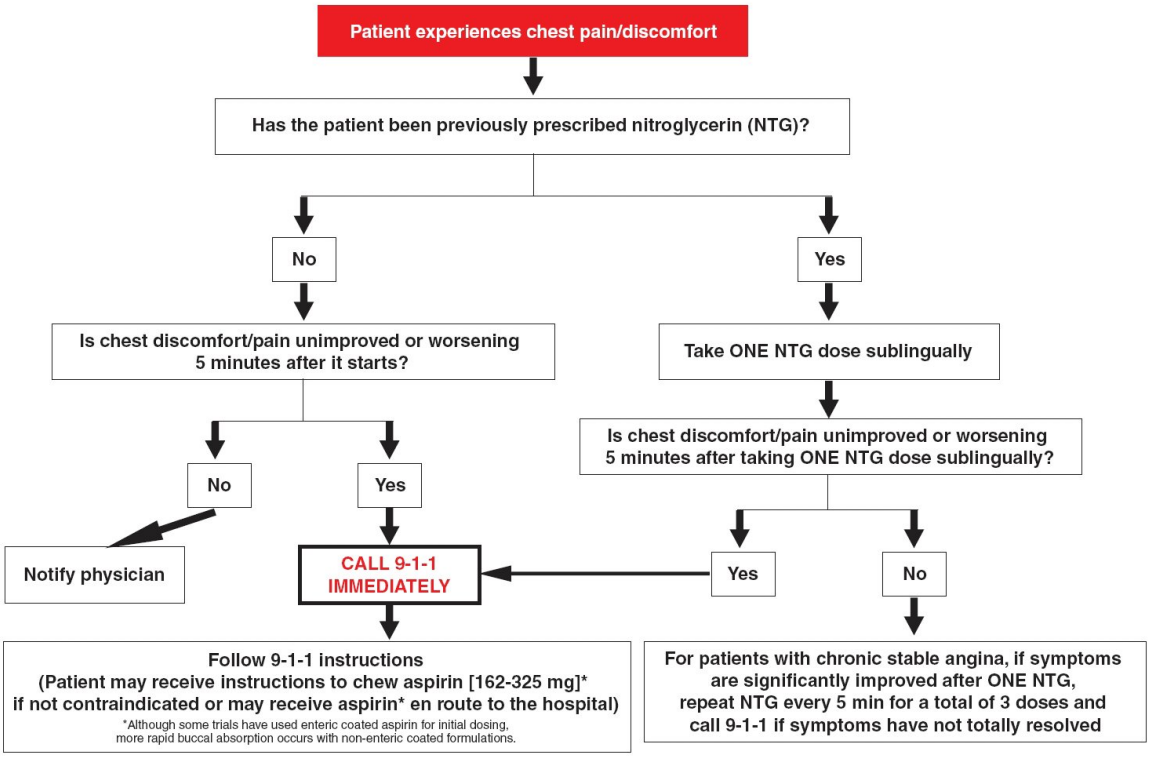
Nitrates should not be used in patients with:

- Initial systolic blood pressure <90 mm Hg, or 30 mm Hg below baseline
- Severe bradycardia (<50 beats per min)
- Tachycardia (>100 beats per min) in the absence of symptomatic heart failure
- Right ventricular (RV) infarction. Nitroglycerin should only be used with extreme caution, if at all, in patients with suspected inferior wall MI with possible RV involvement, as these patients require adequate RV preload
- Erectile dysfunction who received a phosphodiesterase inhibitor within the previous 24 hours (sildenafil) or 48 hours (tadalafil). The suitable time for administering nitrates after vardenafil has not been determined

Instructions for patients

Patients with chronic stable angina or post-ACS should be familiar with ACC/AHA instructions on the appropriate use of nitroglycerin spray or tablets, as well as when to contact the healthcare system (Figure 1).

Figure 1. Instructions for Patients With Chronic Stable Angina or Post-UA ACS



Nitroglycerin Formulations: Tablet vs Spray

Two commonly used formulations of nitroglycerin are tablet and spray. These methods of delivery differ in several therapeutic parameters that may affect their efficacy and tolerability (Table 3).

Onset of the Vasodilatory Response

Results of clinical trials demonstrate that lingual nitroglycerin spray is associated with a more rapid onset of vasodilation and, hence, pain relief. A randomized controlled study by Vandenberg et al of 352 patients compared nitroglycerin tablets and spray, self-administered according to a predetermined schedule. When queried about how quickly pain relief occurred, nearly twice as many patients who received spray reported that their pain was relieved immediately or within 1 minute (70% vs 38% for tablets, $P<0.001$). Twenty-one percent of patients reported immediate relief with spray compared with 11% of patients who used nitroglycerin sublingual tablets. A large comparative study, enrolling nearly 800 patients, was performed in the general-practice setting by Wright et al. This study reported that 62% of patients treated with the spray formulation gained relief in under 1 minute compared with 36% of patients receiving tablets ($P<0.001$). This clinical benefit was reported in both elderly (≥65 years of age) and younger patients.

In a randomized controlled study, significantly more patients treated with nitroglycerin lingual spray (70%) reported that their pain was relieved in less than 60 seconds when compared with those who received tablets (38%).

Other studies have assessed objective (ie, non–patient-reported) responses to nitroglycerin including a study by Laslett et al that evaluated the timing of hemodynamic alterations in 49 patients undergoing elective diagnostic cardiac catheterization. The reduction of left ventricular end-diastolic pressure was similar for both sublingual formulations; however, a significant degree of pressure reduction occurred earlier for the spray formulation compared with tablets (1.5 vs 2 minutes). Using brachial artery ultrasound in normal volunteers, Ducharme et al measured the rapidity of onset, as well as the magnitude and duration, of the vasodilatory effect of both formulations. The spray had a significantly faster onset of action, as reflected in brachial artery diameter at 2 minutes ($P=0.0002$ vs baseline). In addition, the magnitude of response was significantly greater compared with tablets at all time points: 2 minutes ($P=0.01$), 4 minutes ($P=0.009$), and 15 minutes ($P=0.005$) after administration.

These pharmacodynamic results are consistent with the concept that a spray formulation eliminates the time required for tablet dissolution, which may vary from patient to patient. Together, these studies suggest that nitroglycerin that is sprayed directly onto or under the tongue and directly absorbed offers patients more rapid relief—sometimes immediate—of angina pain compared with sublingual tablets (Table 2).

Incidence of Headache

Headache is the most common side effect in all nitrate therapies. Fortunately, this reaction may occasionally abate during the course of therapy even when the anti-anginal efficacy is maintained. Of note, the incidence of headache varies by nitroglycerin formulation. The randomized controlled study by Vandenberg et al discussed earlier reported that significantly fewer patients treated with nitroglycerin lingual spray reported moderate or severe headache (7%) compared with those who received tablets (21%; $P<0.001$).

Storage and Stability

In a randomized controlled study, significantly fewer patients treated with nitroglycerin lingual spray (7%) reported moderate or severe headache as compared with those who received tablets (21%).

Nitroglycerin (glyceryl trinitrate) is inherently unstable and subject to chemical degradation if not stored properly. Studies from more than 30 years ago documented the stability issues associated with nitroglycerin sublingual tablets in that both compressed and molded forms of commercially available tablets showed significant, temperature-dependent (ie, room temperature vs 50°C) loss of potency over time. This occurred even if bottles remained unopened during storage. Exposure of nitroglycerin to atmospheric heat, light, and moisture can be expected to cause even greater loss of potency. Tablets carried by patients after transfer from the manufacturer's original bottle to other "airtight" containers were shown to contain significantly lower therapeutic concentrations of nitroglycerin compared with fresh tablets. Pill boxes were even less effective for storage and their use should be discouraged.

The recommended shelf life of nitroglycerin differs by formulation; 12 weeks for tablets and up to 2 to 3 years for sprays. A survey undertaken at 9 cardiac rehabilitation centers revealed that, among the 79% of patients who routinely carried nitroglycerin on their person, 15% had tablets that were 7 to 12 months old, and tablet age exceeded a full year in 23%.

Table 3. Comparison of Nitroglycerin Formulations: Onset of Action, Tolerability, and Ease of Application

	Lingual Spray	Sublingual Tablets
Onset of action (diastolic blood pressure)	1.5 minutes	2.0 minutes
Onset of vasodilation (brachial artery diameter)	Significantly faster	Significantly slower
Time to dissolution	N/A	May vary patient to patient
Effect of dry mouth	N/A	May slow tablet dissolution
Pain relief in <1 minute	70%*	38%
Moderate or severe headache	7%*	21%
Ease of application/use	1 or 2 metered sprays	Locating, opening, and recapping a small bottle

*$P<0.001$, spray vs tablets.

Spray Device Configuration and Administration

Nitroglycerin lingual spray formulations are currently available in two distinct device configurations that differ in design and use (Table 4). NitroMist® (nitroglycerin lingual aerosol) is fully sealed at manufacture, with inert nonchlorofluorocarbon (CFC) propellant added. The closed system represents an important advance, ensuring consistent delivery of nitroglycerin with a 36-month shelf life. Nitrolingual® Pumpspray (nitroglycerin lingual spray) is packaged in a glass bottle that is not a closed system. The shelf life of this product is 24 months.

Administration of nitroglycerin lingual spray also differs between these devices. NitroMist uses a novel, patented valve technology designed to deliver a consistent dose (400 mcg) at each actuation. Adequate pressure must be applied to activate the metered valve. To administer, the actuator button is pressed firmly with the forefinger, delivering one or two sprays. The metered valve forces the product to the buccal area where absorption occurs. Nitrolingual Pumpspray (nitroglycerin lingual spray) is a metered pump spray. For administration, the patient is directed to press the spray button firmly with the forefinger, delivering one or two sprays. As with NitroMist, adequate pressure must be applied to activate the metered valve.

Nitroglycerin lingual spray formulations offer ease of administration compared with small tablets (approximately 4 mm in diameter) that must be extracted from a correspondingly small bottle, at times in the dark. Ease of use is especially important for relief of angina, when a patient may be experiencing anxiety in addition to pain or clenching their teeth.

Table 4. Comparison of Nitroglycerin Devices: Design and Use

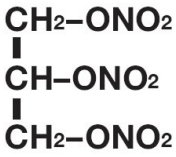
NitroMist® (nitroglycerin lingual aerosol)	Nitrolingual® Pumpspray* (nitroglycerin lingual spray)
Propellant-driven ultrafine mist via metered dose ensures consistent delivery†	Volume sprayed depends on pressure applied
Adequate pressure must be applied to activate metered valve	Adequate pressure must be applied to activate metered valve
Contains soothing menthol, which also enhances oral transmucosal absorption	Contains 20% ethanol
36-month shelf life	24-month shelf life

*Nitrolingual Pumpspray is a registered trademark of First Horizon Pharmaceutical Corporation.
†Delivery technology does not necessarily affect clinical outcomes.

Introduction to NitroMist®

Product Description

Nitroglycerin, an organic nitrate, is a vasodilator that has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate ($C_3H_5N_3O_9$). The compound has a molecular weight of 227.09. The chemical structure is:



NitroMist (nitroglycerin) lingual aerosol is a metered-dose spray containing 230 metered sprays of nitroglycerin. This product delivers 400 mcg of nitroglycerin per actuation in the form of spray droplets on or under the tongue. Inactive ingredients: caprylic/capric diglycerol succinate, peppermint oil, L(-)-menthol, n-butane.

Indications and Usage

NitroMist is indicated for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease.

Dosage and Administration

Recommended dosage

At the onset of an attack, one or two metered sprays should be administered on or under the tongue. A spray may be repeated approximately every 5 minutes as needed. If 2 sprays are used initially, the patient may only administer 1 more spray after waiting 5 minutes. No more than 3 metered sprays are recommended within a 15-minute period. If chest pain persists after a total of 3 sprays, prompt medical attention is recommended. NitroMist may be used prophylactically 5 to 10 minutes before engaging in activities that might precipitate an acute attack.

Priming the container

After an initial priming of 10 sprays, each metered spray of NitroMist delivers 33 mg of solution containing 400 mcg of nitroglycerin. It will remain adequately primed for 6 weeks. If the product is not used within 6 weeks, it can be adequately re-primed with 2 sprays. There are 230 metered sprays per container, but the total number of available doses depends on the number of sprays per use (1 or 2 sprays), and the frequency of priming.

Administration

During use the patient should rest, ideally in the sitting position. The container should be held vertically with the valve head uppermost and the spray orifice as close to the mouth as possible. The dose should preferably be sprayed into the mouth on or under the tongue by pressing the button firmly and the mouth should be closed immediately after each dose. THE SPRAY SHOULD NOT BE INHALED. Patients should be instructed to familiarize themselves with the position of the spray orifice, which can be identified by the finger rest on top of the valve, in order to facilitate orientation for administration at night.

1. Do not shake container.
2. Remove plastic cap.
3. If this is the first time using the bottle, press actuator button 10 times to ensure proper dose priming (holding unit away from yourself and others).
4. Hold container upright with forefinger on top of the actuator button.
5. Open mouth and bring the container as close as possible.
6. Press the actuator button firmly with forefinger to release spray onto or under the tongue.
7. Release button and close mouth. The medication should not be spit out or the mouth rinsed for 5 to 10 minutes following administration.
8. If a second administration is required to obtain relief, repeat steps 4, 5, and 6. No more than 3 metered sprays can be given within a 15-minute period.
9. Replace plastic cover.
10. If the product is not used for more than 6 weeks, then it can be adequately re-primed with 2 sprays.

The level of the liquid in the container should be periodically checked. While the container is in the upright position, if the liquid reaches the top or middle of the hole on the side of the container, one should order more. When the liquid reaches the bottom of the hole, the remaining doses will have less than label content.

Dosage forms and strengths

Lingual aerosol, 400 mcg per spray, 230 metered sprays per container.

Clinical Pharmacology

Mechanism of action

Nitroglycerin forms free radical nitric oxide (NO), which activates guanylate cyclase, resulting in an increase of guanosine 3',5'-monophosphate (cyclic GMP) in smooth muscle and other tissues. This eventually leads to dephosphorylation of myosin light chains, which regulates the contractile state in smooth muscle and results in vasodilatation.

Pharmacodynamics

The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle. Although venous effects predominate, nitroglycerin produces, in a dose-related manner, dilation of both arterial and venous beds. Dilation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood, decreases venous return to the heart, and reduces left ventricular end-diastolic pressure (preload). Nitroglycerin also produces arteriolar relaxation, thereby reducing peripheral vascular resistance and arterial pressure (after load), and dilates large epicardial coronary arteries; however, the extent to which this latter effect contributes to the relief of exertional angina is unclear.

Therapeutic doses of nitroglycerin may reduce systolic, diastolic, and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases diastolic filling time.

Elevated central venous and pulmonary capillary wedge pressures, and pulmonary and systemic vascular resistance are also reduced by nitroglycerin therapy. Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Cardiac index may be increased, decreased, or unchanged. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased and a more favorable supply/demand ratio can be achieved. Patients with elevated left ventricular filling pressure and increased systemic vascular resistance in association with a depressed cardiac index are likely to experience an improvement in cardiac index. In contrast, when filling pressures and cardiac index are normal, cardiac index may be slightly reduced following nitroglycerin administration.

Pharmacokinetics

Nitroglycerin is rapidly absorbed following lingual spray administration. In a pharmacokinetic study when a single 1200 mcg dose (three activations of a 400 mcg dose) of NitroMist was administered to healthy volunteers (n=12), all subjects had detectable trinitroglycerin plasma levels (mean C_{max} 0.8 ± 0.7 ng/mL and t_{max} of 8 min, range 4 to 15 min) beginning at 2 minutes post-dose and higher levels of the 1,2- (mean C_{max} 3.7 ± 1 ng/mL and t_{max} 34 ± 21 min, range 15 to 90 min) and 1,3-dinitroglycerin metabolites (mean C_{max} 1 ± 0.3 ng/mL and mean t_{max} 41 ± 20 min, range 20 to 90 min).

The volume of distribution of nitroglycerin following intravenous administration is 3.3 L/kg.

A liver reductase enzyme is of primary importance in the metabolism of nitroglycerin to glycerol di- and mononitrate metabolites and ultimately to glycerol and organic nitrate. Known sites of

extrahepatic metabolism include red blood cells and vascular walls. In addition to nitroglycerin, 2 major metabolites, 1,2- and 1,3-dinitroglycerin are found in plasma. The mean elimination half-life of both 1,2- and 1,3-dinitroglycerin is about 40 minutes. The 1,2- and 1,3-dinitroglycerin metabolites have been reported to possess some pharmacological activity, whereas the glycerol mononitrate metabolites of nitroglycerin are essentially inactive. Higher plasma concentrations of the dinitro metabolites, with their nearly 8-fold longer elimination half-lives, may contribute significantly to the duration of pharmacologic effect.

In the above-referenced pharmacokinetic study the average initial half-lives ($T_{½\alpha}$) of nitroglycerin, and its 1,2- and 1,3-dinitroglycerin metabolites were estimated to be 3, 10, and 11 minutes, respectively. The half-life of disappearance of the nitroglycerin ($T_{½\beta}$) (5 minutes) was significantly less than the half-life of appearance ($T_{½\alpha}$) of the 1,2- and 1,3-dinitroglycerin metabolites suggesting the possibility of an additional compartment into which the nitroglycerin disappears from plasma prior to being metabolized into the dinitroglycerin metabolites. A second indication of this other compartment is that the appearance of nitroglycerin metabolites in plasma was delayed in some subjects, with zero plasma levels seen for 4-6 minutes after dosing. In some subjects, nitroglycerin metabolites appeared only after nitroglycerin C_{max} had been observed.

Clinical Studies

In a randomized, double-blind, single-center, single-administration, placebo-controlled, 4-period cross-over study in 30 subjects with stable angina pectoris, statistically significant dose-related increases in exercise tolerance were seen following doses of 200, 400, and 800 mcg of nitroglycerin delivered by NitroMist compared with placebo.

Contraindications

PDE5 inhibitor use

Administration of NitroMist is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), as PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates (see Drug Interactions).

Severe anemia

NitroMist is contraindicated in patients with severe anemia.

Increased intracranial pressure

NitroMist is contraindicated in patients with increased intracranial pressure.

Hypersensitivity

NitroMist is contraindicated in patients who have shown hypersensitivity to it or to other nitrates or nitrites. Skin reactions consistent with hypersensitivity have been observed with organic nitrates.

Warnings and Precautions

Tolerance

Excessive use may lead to the development of tolerance. Only the smallest number of doses required for effective relief of the acute anginal attack should be used (see Dosage and Administration).

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is reduced.

Hypotension

Severe hypotension, particularly with upright posture, may occur even with small doses of nitroglycerin. The drug should therefore be used with caution in patients who may be volume-depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

The benefits of NitroMist in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use NitroMist in these conditions, careful clinical or hemodynamic monitoring must be used because of the possibility of hypotension and tachycardia.

Hypertrophic cardiomyopathy

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Headache

Nitroglycerin produces dose-related headaches, which may be severe. Tolerance to headaches rarely occurs.

Adverse Reactions

Headache, which may be severe and persistent, may occur immediately after nitroglycerin use.

Flushing, drug rash and exfoliative dermatitis have been reported in patients receiving nitrate therapy.

Postural hypotension, as manifest by vertigo, weakness, palpitation, and other symptoms, may develop occasionally, particularly in erect, immobile patients. Marked sensitivity to the hypotensive effects of nitrates (manifested by nausea, vomiting, weakness, diaphoresis, pallor, and collapse) may occur at therapeutic doses.

Syncope due to nitrate vasodilatation has been reported.

Drug Interactions

PDE5 inhibitors

Administration of NitroMist is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates.

The time course and dose dependence of this interaction have not been studied, and use within a few days of one another cannot be recommended. Appropriate supportive care for the severe hypotension has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion. The use of any form of nitroglycerin during the early days of acute myocardial infarction requires particular attention to hemodynamic monitoring and clinical status.

Antihypertensives

Patients receiving antihypertensive drugs, beta-adrenergic blockers, and nitrates should be observed for possible additive hypotensive effects. Marked orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used concomitantly.

Labetalol blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effects. If labetalol is used with nitroglycerin in patients with angina pectoris, additional hypotensive effects may occur.

Aspirin

Coadministration of aspirin and nitroglycerin has been reported to result in increased nitroglycerin maximum concentrations by as much as 67% and AUC by 73% when administered as a single dose. The vasodilatory and hemodynamic effects of nitroglycerin may be enhanced by concomitant administration of aspirin.

Tissue-type plasminogen activator

Intravenous administration of nitroglycerin decreases the thrombolytic effect of tissue-type plasminogen activator (t-PA). Plasma levels of t-PA are reduced when coadministered with nitroglycerin. Therefore, caution should be observed in patients receiving nitroglycerin during t-PA therapy.

Heparin

Intravenous nitroglycerin reduces the anticoagulant effect of heparin. Activated partial thromboplastin time (aPTT) should be monitored in patients receiving heparin and intravenous nitroglycerin. It is not known if this effect occurs following single nitroglycerin doses.

Ergotamine

Oral administration of nitroglycerin markedly decreases the first-pass metabolism of dihydroergotamine and subsequently increases its oral bioavailability. Ergotamine is known to precipitate angina pectoris. Therefore, patients receiving sublingual nitroglycerin should avoid ergotamine and related drugs or be monitored for symptoms of ergotism if this is not possible.

Use in Specific Populations

Pregnancy

Pregnancy category C: Animal reproduction and teratogenicity studies have not been conducted with NitroMist or nitroglycerin sublingual tablets. It is also not known whether NitroMist can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. A teratogenicity study was conducted in the third mating of F_0 generation female rats administered dietary nitroglycerin for gestation days 6 to 15 at dose levels used in the 3-generation reproduction study. In offspring of the high-dose nitroglycerin group, increased incidence of diaphragmatic hernias and decreased hyoid bone ossification were seen. The latter finding probably reflects delayed development rather than a potential teratogenic effect, thus indicating no clear evidence of teratogenicity of nitroglycerin.

There are no adequate and well-controlled studies in pregnant women. NitroMist should be given to a pregnant woman only if clearly needed.

Nursing mothers

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NitroMist is administered to a nursing woman.

Pediatric use

The safety and effectiveness of nitroglycerin in pediatric patients have not been established.

Geriatric use

Clinical studies of NitroMist did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly (>65 years) and younger (≤65 years) patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Overdosage

Signs and symptoms of hemodynamic effects: The effects of nitroglycerin overdose are generally the results of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations including increased intracranial pressure with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; tachycardia; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); dyspnea, later followed by reduced ventilatory effort, diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is not recommended.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia: Methemoglobinemia has been rarely reported with organic nitrates. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate arterial PO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

If methemoglobinemia is present, intravenous administration of methylene blue, 1 to 2 mg/kg of body weight, may be required.

Nonclinical Toxicology

Carcinogenesis, mutagenesis, impairment of fertility

Animal carcinogenicity studies with sublingually administered or lingual spray nitroglycerin have not been performed.

Rats receiving up to 434 mg/kg/day of dietary nitroglycerin for 2 years developed dose-related fibrotic and neoplastic changes in liver, including carcinomas, and interstitial cell tumors in testes. At the highest dose, the incidences of hepatocellular carcinomas was 52% compared to 0% in untreated controls. Incidences of testicular tumors were 52% vs 8% in controls. Lifetime dietary administration of up to 1058 mg/k/day of nitroglycerin was not tumorigenic in mice.

Nitroglycerin was found to have reverse mutation activity in the *Salmonella typhimurium* strain TA1535 (Ames assay). A similar mutation in *S. typhimurium* strain was also reported for other NO donors. Nevertheless, there was no evidence of mutagenicity in an *in vivo* dominant lethal assay with male rats treated with oral doses of up to about 363 mg/kg/day or in *ex vitro* cytogenic tests in rat and dog tissues. *In vitro* cytogenetic assay using Chinese hamster ovary cells showed no chromosomal aberrations.

In a 3-generation reproduction study, rats received dietary nitroglycerin at doses up to about 408 mg/kg/day (males) to 452 mg/kg/day (females) for 5 months (females) or 6 months (males) prior to mating of the F_0 generation with treatment continuing through successive F_1 and F_2 generations. The highest dose was associated with decreased feed intake and body weight gain in both sexes at all matings. No specific effect on the fertility of the F_0 generation was seen. Infertility noted in subsequent generations, however, was attributed to increased interstitial cell tissue and aspermatogenesis in the high-dose males.

How Supplied

Each box of NitroMist contains one glass bottle coated with red/orange transparent plastic which assists in containing the glass and medication should the bottle be shattered. Each unit contains 8.5 g (net content) of nitroglycerin lingual aerosol and will deliver 230 metered sprays containing 400 mcg of nitroglycerin per actuation.

NDC 24090-410-08

Storage and Handling

Storage: Store at room temperature (25°C, 77°F); excursions permitted to 15-30°C (59-85°F)

Handling: NitroMist contains a highly flammable propellant (butane). Do not forcefully open a NitroMist bottle, do not have the container burned after use, and do not spray directly toward flames.

Cost Considerations

There are several factors to be considered when choosing a nitroglycerin product (Table 5).

Table 5. Commercially Available Nitroglycerin Lingual Sprays

	NDC #	WAC	Package Size
NitroMist® (nitroglycerin lingual aerosol, 400 mcg/spray)	24090-410-08		230-metered spray (8.5 g) single bottle
Nitrolingual® Pumpspray (nitroglycerin lingual spray, 0.4 mg per spray)	59630-300-65 59630-300-20 59630-300-26		60-metered spray (4.9 g) single bottle 200-metered spray (12 g) single bottle Duo Pack (one 4.9 g and one 12 g bottle)

Nitrolingual is a registered trademark of G. Pohl-Boskamp GMBH & Co.

Conclusion

The use of nitroglycerin remains a cornerstone of therapy for patients suffering from acute episodes of angina as well as for those with a history of angina who require prophylaxis prior to exertion and/or stress. Regardless of the setting, both institution and at home, nitroglycerin remains the single best medication for the relief of acute angina.

There are important differences between sublingual tablets and lingual spray formulations when it comes to both efficacy and adverse effects. As highlighted in this dossier, lingual spray formulations have been associated with a faster onset of action (by patient reports and clinical measures from heart catheterizations and brachial artery diameter) and a lower incidence of headache, the primary adverse event associated with sublingual nitroglycerin.

Furthermore, due to the unstable nature of sublingual tablets, the difficulties some patients have in accessing their tablets during an episode of angina, and the risks associated with carrying subpotent or outdated tablets, nitroglycerin lingual spray offers patients simple ease-of-use and the confidence of potency and stability for up to 36 months.

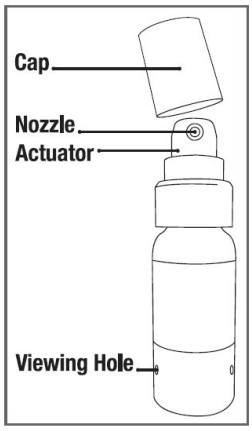
With its fully sealed manufactured system, consistent actuation method, and significantly lower WAC, NitroMist® (nitroglycerin lingual aerosol) offers your patients a highly effective, safe, and well-tolerated lingual spray option for the acute treatment and prophylaxis of angina that is simple to use and provides potency and stability for up to 36 months.

Patient Counseling Information

PATIENT INSTRUCTIONS FOR USE

NitroMist® [nī-trō-mĭst]

(nitroglycerin) lingual aerosol



Important: for use on or under the tongue. Do not inhale.

Read these Patient Instructions For Use before you start using your **NitroMist®**, and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Priming NitroMist spray

Before you use NitroMist spray for the first time, you must prime it. To prime your NitroMist spray, follow the steps below:

- Do not shake the container.
- Remove the plastic cap from the container (Figure A).
- While holding the container away from yourself and others, press the actuator button 10 times (Figure B).
- Your NitroMist spray is now primed. You are ready to give your first dose.
- If you do not use your NitroMist spray for more than 6 weeks, you will need to prime again by pressing the nozzle button 2 times.

Figure A

Figure B

N 3 24090-410-08 3

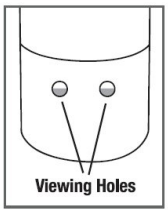
Giving a dose

1. Hold your NitroMist spray upright with your index finger on top of the actuator button.
2. Open your mouth and bring the NitroMist spray as close as possible to your mouth.
3. Press the actuator button firmly to release the NitroMist spray(s) onto or under your tongue (Figure C).
4. Release the actuator button and close your mouth. Do not spit out NitroMist or rinse your mouth for 5 to 10 minutes after using NitroMist.
5. If a second dose is needed, repeat steps 1-4.
6. Replace the plastic cap (Figure D).

Figure C

Figure D

You should check the level of the fluid in your NitroMist container regularly. Check the container in an upright position. When the fluid level reaches the top or middle of the hole on the side of the container you should get a refill.



How should I store NitroMist?

- Store NitroMist upright at room temperature 59° F to 85° F (15°C to 30°C).
- NitroMist is flammable. **Do not burn the NitroMist container after use, and do not spray directly toward flames.**
- Do not forcefully open a NitroMist container.

Keep NitroMist and all medicines out of the reach of children.

AKRIMAX
PHARMACEUTICALS

Manufactured for Akrimax Pharmaceuticals, LLC
Cranford, NJ 07016
By Dynamit Nobel GmbH, Leverkusen, Germany

Marketed and Distributed by: Akrimax Pharmaceuticals, LLC
Cranford, NJ 07016 USA

NDC 24090-410-08

0841P001
Rev. November 2010

References

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Notes

Notes

Notes

Notes

NITROMIST®
Nitroglycerin Lingual Aerosol • 400 mcg/spray

AKRIMAX
PHARMACEUTICALS

EXHIBIT E

You should check the level of the fluid in your NitroMist container regularly. Check the container in an upright postion. When the fluid level reaches the top or middle of the hole on the side of the container, you should get a refill.

INDICATIONS AND USAGE
NitroMist is indicated for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease.

DOSAGE FORMS AND STRENGTHS
Lingual aerosol, 400 mcg per spray, 230 metered sprays per container.

CONTRAINDICATIONS
Administration of NitroMist is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), as PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates.

NitroMist is contraindicated in patients with severe anemia.

WARNINGS AND PRECAUTIONS
Excessive use may lead to the development of tolerance. Only the smallest number of doses required for effective relief of the acute anginal attack should be used.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is reduced.

Please see full Prescribing Information at www.nitromist.com.

References: 1. Vandenburg MJ, Griffiths GK, Brandman S. Sublingual nitroglycerin or spray in the treatment of angina. *Br J Clin Pract.* 1986;40(12):524-527. **2.** Data on file, 1996, Akrimax Pharmaceuticals, LLC.

AKRIMAX PHARMACEUTICALS

NTR-056-1 January 2011

NITROMIST
Nitroglycerin Lingual Aerosol • 400 mcg/spray

The benefits of nitroglycerin aerosol delivery—
and significant savings on your prescription

Pay No More Than
$20
for your next NitroMist prescription

Emdeon Therapy First Plus
BIN# 004682
PCN# CN
GRP# EC54002001
ID# 38423375458

LoyaltyRx

NITROMIST
Nitroglycerin Lingual Aerosol • 400 mcg/spray

2442-25

NitroMist

Nitroglycerin Lingual Aerosol • 400 mcg/spray

NitroMist is indicated for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease.

Nitroglycerin aerosol spray provides rapid relief from acute angina, delivering symptom relief in less than 60 seconds in a majority of patients.[1]

NitroMist provides everyday prophylaxis of exercise-induced angina. It significantly increases exercise tolerance time (time to onset of symptoms) in patients with stable angina, compared with placebo ($P<.0001$).[2] NitroMist may be used 5 to 10 minutes before engaging in activities that may precipitate an attack.

NitroMist is designed to deliver a consistent and fully effective 400-mcg dose. Adequate pressure must be applied to the actuator button to activate the metered dose.

NitroMist is convenient, reliable, and easy to use. The NitroMist bottle is distinct and easy to recognize. The pocket-sized aerosol delivery system provides convenience and reliability, maintaining potency and stability for up to 3 years.

Taking your NitroMist

Acute angina can strike at any time. Taking your NitroMist correctly is critical to getting the full benefits from the medication.

First, Prime Your NitroMist Bottle

Remove the plastic cap and hold the bottle away from yourself and others.

Place your forefinger in the finger rest at the top of the actuator valve and press the actuator 10 times. The bottle is now primed for 6 weeks and ready for use. If NitroMist is not used for more than 6 weeks, the bottle can be reprimed with 2 sprays before using.

Taking NitroMist During an Acute Angina Episode

Ideally, you should be in a sitting position when taking NitroMist.

Remove the plastic cap. Hold the bottle upright and place your forefinger in the finger rest at the top of the actuator button.

Open your mouth and bring the spray opening as close to your mouth as possible.

Press the actuator button to spray NitroMist on or under your tongue. Release the button and close your mouth. Do not inhale the medication. Do not spit out any medication or rinse your mouth for 5 to 10 minutes after taking NitroMist.

If a second dose is required for relief, a spray may be repeated approximately every 5 minutes as needed. No more than 3 metered sprays are recommended within a 15-minute period. If chest pain persists after 3 sprays, you should seek prompt medical attention. When finished using NitroMist, replace the plastic cap.

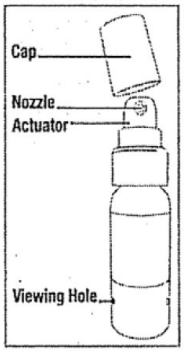
EXHIBIT F

PATIENT INSTRUCTIONS FOR USE

NitroMist® [ni-trō-mist]

(nitroglycerin) lingual aerosol

Important: for use on or under the tongue. Do not inhale.



Read these Patient Instructions For Use before you start using your NitroMist®, and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Priming NitroMist spray

Before you use NitroMist spray for the first time, you must prime it. To prime your NitroMist spray, follow the steps below:

Figure A

- Do not shake the container.
- Remove the plastic cap from the container (Figure A).

Figure B

- While holding the container away from yourself and others, press the actuator button 10 times (Figure B).
- Your NitroMist spray is now primed. You are ready to give your first dose.
- If you do not use your NitroMist spray for more than 6 weeks, you will need to prime again by pressing the nozzle button 2 times.

N 3 24090-410-08 3

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Giving a dose

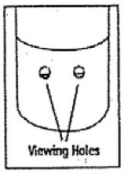
Figure C

1. Hold your NitroMist spray upright with your index finger on top of the actuator button.
2. Open your mouth and bring the NitroMist spray as close as possible to your mouth.
3. Press the actuator button firmly to release the NitroMist spray(s) onto or under your tongue (Figure C).

Figure D

4. Release the actuator button and close your mouth. Do not spit out NitroMist or rinse your mouth for 5 to 10 minutes after using NitroMist.
5. If a second dose is needed, repeat steps 1-4.
6. Replace the plastic cap (Figure D).

You should check the level of the fluid in your NitroMist container regularly. Check the container in an upright position. When the fluid level reaches the top or middle of the hole on the side of the container you should get a refill.



How should I store NitroMist?

- Store NitroMist upright at room temperature 59° F to 85° F (15°C to 30°C).
- NitroMist is flammable. **Do not burn the NitroMist container after use, and do not spray directly toward flames.**
- Do not forcefully open a NitroMist container.

Keep NitroMist and all medicines out of the reach of children.

AKRIMAX PHARMACEUTICALS

Manufactured for Akrimax Pharmaceuticals, LLC
Cranford, NJ 07016
By Dynamit Nobel GmbH, Leverkusen, Germany

Marketed and Distributed by: Akrimax Pharmaceuticals, LLC
Cranford, NJ 07016 USA

NDC 24090-410-08

0841P001
Rev. November 2010

EXHIBIT G

Nitrolingual® Pumpspray

(nitroglycerin lingual spray)
400 mcg per spray, 60 or 200 Metered Sprays

Before using your Nitrolingual® Pumpspray (nitroglycerin lingual spray) 400 mcg per spray, 60 or 200 metered sprays, read carefully the following directions for use.

Nitrolingual® Pumpspray is a metered dose spray which delivers 48 mg of solution containing 400 mcg of nitroglycerin with each spray. Nitroglycerin is absorbed from the tongue and surrounding mucosa producing a prompt therapeutic effect. It is best to use Nitrolingual® Pumpspray in a sitting position.

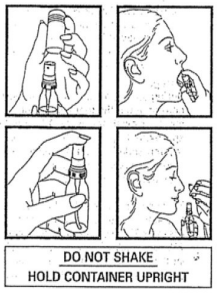
NL-PS-PI-6 Rev. 10/08

INFORMATION FOR THE PATIENT

How to Use Nitrolingual® Pumpspray

Before using this product for the first time, the pump must be sprayed 5 times into the air (this is known as priming). The pump should be primed every 6 weeks to remain ready for use. If the product has not been used for 6 weeks, a prime of 1 spray is necessary.

1. Remove the plastic cover.
2. DO NOT SHAKE.
3. Hold the container upright with forefinger on top of the grooved button.
4. Open the mouth and bring the container as close to it as possible.
5. Press the button firmly with the forefinger to release the spray onto or under the tongue. DO NOT INHALE THE SPRAY.
6. Release button and close mouth. Avoid swallowing immediately after administering the spray. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration.
7. If you require a second administration to obtain relief, repeat steps 4, 5, and 6.
8. Replace the plastic cover.



NOTE: To familiarize yourself with the product and while priming the container, actuate the spray into the air (away from yourself and others). Get the feel of your finger resting on the grooved button so that you can use the spray in the dark. **DO NOT SHAKE** the container before use. You may wish to keep additional pumpspray containers handy in convenient locations.

Dosage

During an anginal attack, one or two sprays should be administered into your mouth, preferably onto or under the tongue. Do not inhale spray. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration. A spray may be repeated approximately every 3-5 minutes as needed. No more than three metered sprays are recommended within a 15-minute period. If chest pain persists, prompt medical attention is recommended. Nitrolingual® Pumpspray may be used 5 to 10 minutes prior to engaging in activities which might provoke an acute attack.

There are approximately 60 or 200 metered sprays of nitroglycerin per Nitrolingual® Pumpspray bottle. However, the number of times the medication may be used is dependent on the number of sprays per use (1 or 2 sprays), and frequency of repriming. Each metered spray of Nitrolingual® Pumpspray delivers 400 mcg of nitroglycerin after an initial priming of 5 sprays. The container will remain adequately primed for 6 weeks. If the medication is not used within 6 weeks, it can be adequately reprimed with 1 spray. Longer storage periods without use may require up to 5 repriming sprays.

Precaution

Your physician has determined that this product is likely to help your personal health.
USE THIS PRODUCT AS DIRECTED, BY YOUR PHYSICIAN.
If you have any questions about alternatives, consult with your physician.
Do not share or give your medication to others, particularly those who may appear to be having chest discomfort similar to yours.
Nitrolingual® Pumpspray should be used during an episode of chest pain or may be used 5 to 10 minutes prior to engaging in activities which might provoke an acute attack.
Nitrolingual® Pumpspray is available in a clear glass bottle with a red plastic coating on the exterior. This plastic coating is designed to contain the glass and medication should the bottle be shattered.
The transparent container can be used for continuous monitoring of the consumption. **The end of the pump should be covered by the fluid level.** Once fluid falls below the level of the center tube, sprays will not be adequate and the container should be replaced. As with all other sprays, there is a residual volume of fluid at the bottom of the bottle which cannot be used. Nitrolingual® Pumpspray contains 20% alcohol. Do not forcefully open or burn container. Do not spray toward flames. **Keep in a safe place and out of the reach of children.**
Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

Sciele Pharma, Inc. A SHIONOGI COMPANY

Manufactured for Sciele Pharma, Inc., Atlanta, GA 30328
by G. Pohl-Boskamp GmbH & Co. KG, 25551 Hohenlockstedt, Germany.

EXHIBIT H

-APPLICATION-

Title

Title of Work: Product Instructional Drawing: Woman Operating Pumpspray

Completion/Publication

Year of Completion: 1996

Date of 1st Publication: December 20, 1999 **Nation of 1st Publication:** United States

Author

- **Author:** Brigitte Karp

Author Created: 2-D artwork

Work made for hire: Yes

Citizen of: Germany **Domiciled in:** Germany

Copyright claimant

Copyright Claimant: G. Pohl-Boskamp GmbH & Co. KG

Kieler Strasse 11, 25551 Hohenlockstedt, Germany

Transfer Statement: By written agreement

Rights and Permissions

Organization Name: K&L Gates LLP

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Email: tmboston@klgates.com **Telephone:** 617-261-3100

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Certification

Name: Emily H. Cunningham

Date: February 4, 2011

Registration #:

Service Request #: 1-559667731

Application Date: 02-04-2011 16:47:38

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Mail Certificate

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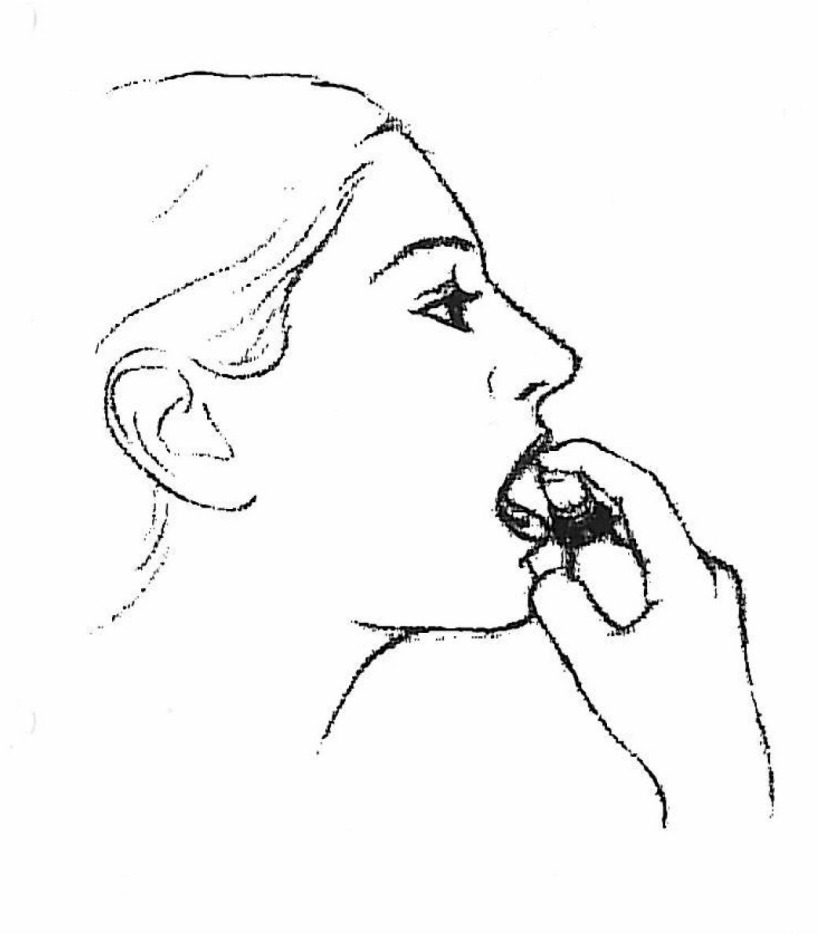

-APPLICATION-

Title

Title of Work: Product Instructional Drawing: Woman and Pumpspray

Completion/Publication

Year of Completion: 1996

Date of 1st Publication: December 20, 1999 **Nation of 1st Publication:** United States

Author

- **Author:** Brigitte Karp

Author Created: 2-D artwork

Work made for hire: Yes

Citizen of: Germany **Domiciled in:** Germany

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Service Request #: 1-559667753

Application Date: 02-04-2011 16:47:49

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-APPLICATION-

Title

Title of Work: Product Instructional Drawing: Hand and Pumpspray

Completion/Publication

Year of Completion: 1996

Date of 1st Publication: December 20, 1999 **Nation of 1st Publication:** United States

Author

- **Author:** Brigitte Karp

Author Created: 2-D artwork

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Email: tmboston@klgates.com **Telephone:** 617-261-3100

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Boston, MA 02111 United States

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Date: February 4, 2011

Registration #:

Service Request #: 1-559569421

Application Date: 02-04-2011 16:47:17

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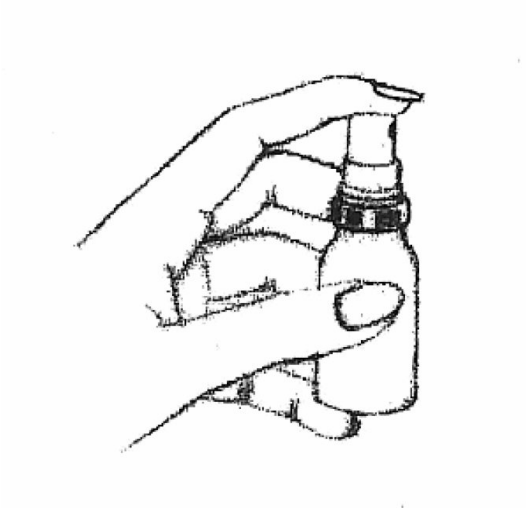
One Lincoln Street
Boston, MA 02111 United States



-APPLICATION-

Title

Title of Work: Product Instructional Drawing: Hand, Cap and Pumpspray

Completion/Publication

Year of Completion: 1996

Date of 1st Publication: December 20, 1999 **Nation of 1st Publication:** United States

Author

- **Author:** Brigitte Karp

Author Created: 2-D artwork

Work made for hire: Yes

Citizen of: Germany **Domiciled in:** Germany

Copyright claimant

Copyright Claimant: G. Pohl-Boskamp GmbH & Co. KG

Kieler Strasse 11, 25551 Hohenlockstedt, Germany

Transfer Statement: By written agreement

Rights and Permissions

Organization Name: K&L Gates LLP

Name: Phi Lan M. Tinsley

Email: tmboston@klgates.com **Telephone:** 617-261-3100

Address: State Street Financial Center

One Lincoln Street

Boston, MA 02111 United States

Certification

Name: Emily H. Cunningham

Date: February 4, 2011

Registration #:

Service Request #: 1-559667609

Application Date: 02-04-2011 16:47:28

Correspondent

Organization Name: K&L Gates LLP

Name: Phi Lan M. Tinsley

Address: State Street Financial Center
One Lincoln Street
Boston, MA 02111 United States

Mail Certificate

K&L Gates LLP
Phi Lan M. Tinsley
State Street Financial Center
One Lincoln Street
Boston, MA 02111 United States

-APPLICATION-

Title

Title of Work: Product Instructional Insert

Completion/Publication

Year of Completion: 1996

Date of 1st Publication: December 20, 1999 **Nation of 1st Publication:** United States

Author

- **Author:** G. Pohl-Boskamp GmbH & Co. KG

Author Created: text

Work made for hire: Yes

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Name: Phi Lan M. Tinsley

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Address: State Street Financial Center

One Lincoln Street

Boston, MA 02111 United States

Certification

Name: Emily H. Cunningham

Date: February 4, 2011

Registration #:

Service Request #: 1-559667785

Application Date: 02-04-2011 16:48:00

Correspondent

Organization Name: K&L Gates LLP

Name: Phi Lan M. Tinsley

Address: State Street Financial Center
One Lincoln Street
Boston, MA 02111 United States

Mail Certificate

K&L Gates LLP
Phi Lan M. Tinsley
State Street Financial Center
One Lincoln Street
Boston, MA 02111 United States

Nitrolingual® Pumpspray

(nitroglycerin lingual spray)
400 mcg per spray, 60 or 200 Metered Sprays

Before using your Nitrolingual® Pumpspray (nitroglycerin lingual spray) 400 mcg per spray, 60 or 200 metered sprays, read carefully the following directions for use.

Nitrolingual® Pumpspray is a metered dose spray which delivers 48 mg of solution containing 400 mcg of nitroglycerin with each spray. Nitroglycerin is absorbed from the tongue and surrounding mucosa producing a prompt therapeutic effect. It is best to use Nitrolingual® Pumpspray in a sitting position.

INFORMATION FOR THE PATIENT

NLPS-PI-5 Rev. 10/08

How to Use Nitrolingual® Pumpspray

Before using this product for the first time, the pump must be sprayed 5 times into the air (this is known as priming). The pump should be primed every 6 weeks to remain ready for use. If the product has not been used for 6 weeks, a prime of 1 spray is necessary.

1. Remove the plastic cover.
2. **DO NOT SHAKE.**
3. Hold the container upright with forefinger on top of the grooved button.
4. Open the mouth and bring the container as close to it as possible.
5. Press the button firmly with the forefinger to release the spray onto or under the tongue. DO NOT INHALE THE SPRAY.
6. Release button and close mouth. Avoid swallowing immediately after administering the spray. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration.
7. If you require a second administration to obtain relief, repeat steps 4, 5, and 6.
8. Replace the plastic cover.

NOTE: To familiarize yourself with the product and while priming the container, actuate the spray into the air (away from yourself and others). Get the feel of your finger resting on the grooved button so that you can use the spray in the dark. **DO NOT SHAKE** the container before use. You may wish to keep additional pumpspray containers handy in convenient locations.

Dosage

During an anginal attack, one or two sprays should be administered into your mouth, preferably onto or under the tongue. Do not inhale spray. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration. A spray may be repeated approximately every 3-5 minutes as needed. No more than three metered sprays are recommended within a 15-minute period. If chest pain persists, prompt medical attention is recommended. Nitrolingual® Pumpspray may be used 5 to 10 minutes prior to engaging in activities which might provoke an acute attack.

There are approximately 60 or 200 metered sprays of nitroglycerin per Nitrolingual® Pumpspray bottle. However, the number of times the medication may be used is dependent on the number of sprays per use (1 or 2 sprays), and frequency of repriming. Each metered spray of Nitrolingual® Pumpspray delivers 400 mcg of nitroglycerin after an initial priming of 5 sprays. The container will remain adequately primed for 6 weeks. If the medication is not used within 6 weeks, it can be adequately reprimed with 1 spray. Longer storage periods without use may require up to 5 repriming sprays.

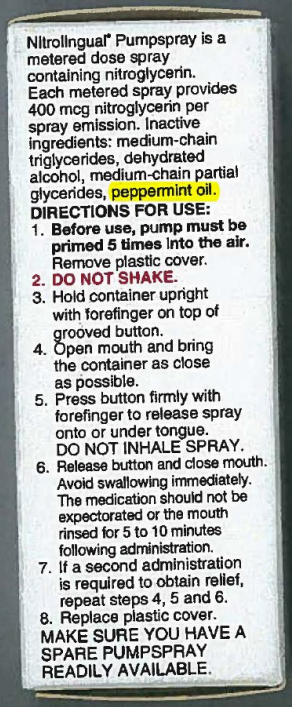
Precaution

Your physician has determined that this product is likely to help your personal health.
USE THIS PRODUCT AS DIRECTED, BY YOUR PHYSICIAN.
If you have any questions about alternatives, consult with your physician.
Do not share or give your medication to others, particularly those who may appear to be having chest discomfort similar to yours.
Nitrolingual® Pumpspray should be used during an episode of chest pain or may be used 5 to 10 minutes prior to engaging in activities which might provoke an acute attack.
Nitrolingual® Pumpspray is available in a clear glass bottle with a red plastic coating on the exterior. This plastic coating is designed to contain the glass and medication should the bottle be shattered.
The transparent container can be used for continuous monitoring of the consumption. **The end of the pump should be covered by the fluid level.** Once fluid falls below the level of the center tube, sprays will not be adequate and the container should be replaced. As with all other sprays, there is a residual volume of fluid at the bottom of the bottle which cannot be used. Nitrolingual® Pumpspray contains 20% alcohol. Do not forcefully open or burn container. Do not spray toward flames. **Keep in a safe place and out of the reach of children.**
Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

Sciele Pharma, Inc. A SHIONOGI COMPANY

Manufactured for Sciele Pharma, Inc., Atlanta, GA 30328
by G. Pohl-Boskamp GmbH & Co. KG, 25551 Hohenlockstedt, Germany.

EXHIBIT C

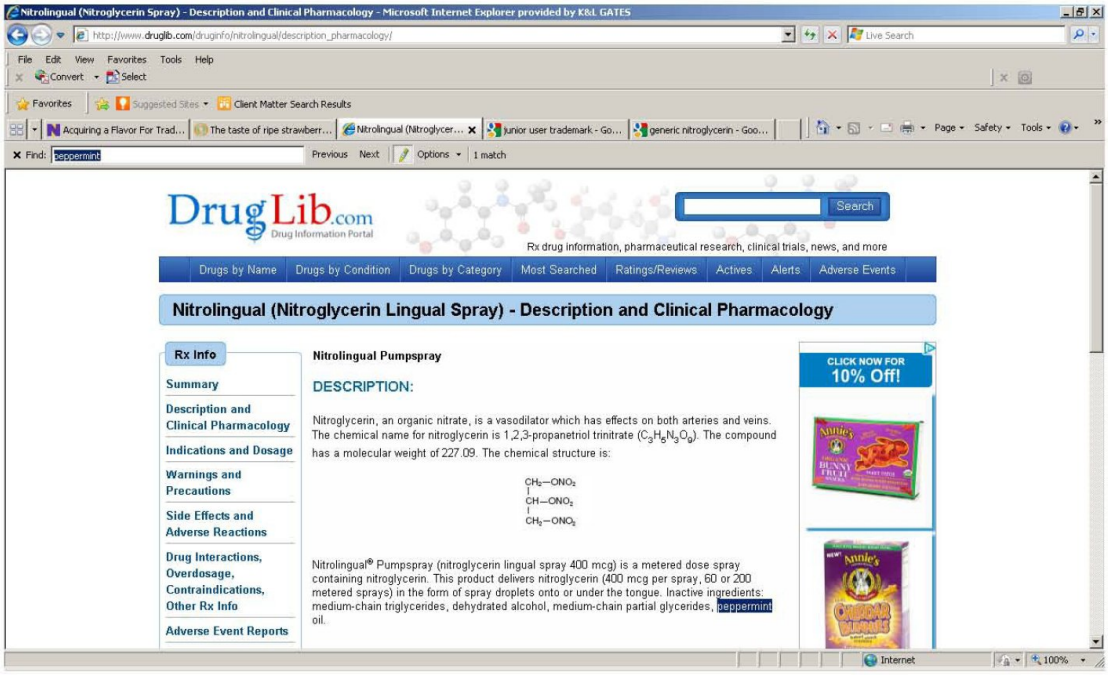


Nitrolingual® Pumpspray is a metered dose spray containing nitroglycerin. Each metered spray provides 400 mcg nitroglycerin per spray emission. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.

DIRECTIONS FOR USE:

1. **Before use, pump must be primed 5 times into the air.** Remove plastic cover.
2. **DO NOT SHAKE.**
3. Hold container upright with forefinger on top of grooved button.
4. Open mouth and bring the container as close as possible.
5. Press button firmly with forefinger to release spray onto or under tongue. DO NOT INHALE SPRAY.
6. Release button and close mouth. Avoid swallowing immediately. The medication should not be expectorated or the mouth rinsed for 5 to 10 minutes following administration.
7. If a second administration is required to obtain relief, repeat steps 4, 5 and 6.
8. Replace plastic cover.

MAKE SURE YOU HAVE A SPARE PUMPSPRAY READILY AVAILABLE.


Nitrolingual (Nitroglycerin Spray) - Description and Clinical Pharmacology - Microsoft Internet Explorer provided by K&L GATES
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Acquiring a Flavor For Trad... The taste of ripe strawberr... Nitrolingual (Nitroglycer... Junior user trademark - Go... generic nitroglycerin - Goo...
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DrugLib.com
Drug Information Portal
Search
Rx drug information, pharmaceutical research, clinical trials, news, and more
Drugs by Name Drugs by Condition Drugs by Category Most Searched Ratings/Reviews Actives Alerts Adverse Events
Nitrolingual (Nitroglycerin Lingual Spray) - Description and Clinical Pharmacology
Rx Info
Summary
Description and Clinical Pharmacology
Indications and Dosage
Warnings and Precautions
Side Effects and Adverse Reactions
Drug Interactions, Overdosage, Contraindications, Other Rx Info
Adverse Event Reports
Nitrolingual Pumpspray
DESCRIPTION:
Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate ($C_3H_5N_3O_9$). The compound has a molecular weight of 227.09. The chemical structure is:
$CH_2—ONO_2$
$CH—ONO_2$
$CH_2—ONO_2$
Nitrolingual® Pumpspray (nitroglycerin lingual spray 400 mcg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.
CLICK NOW FOR 10% Off!
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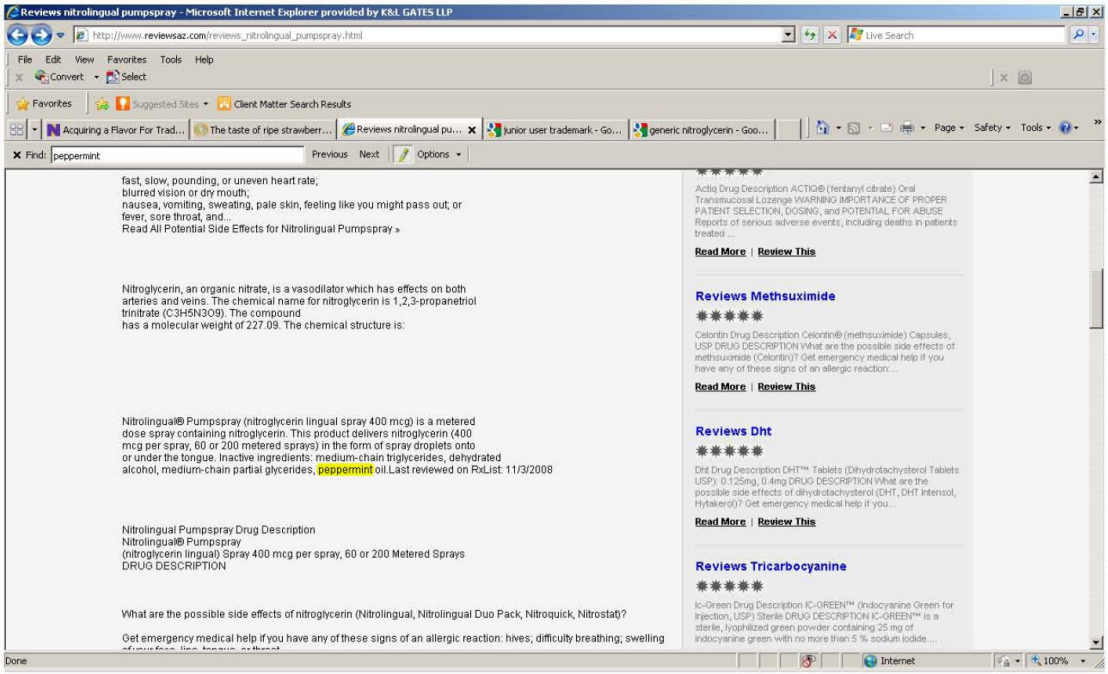
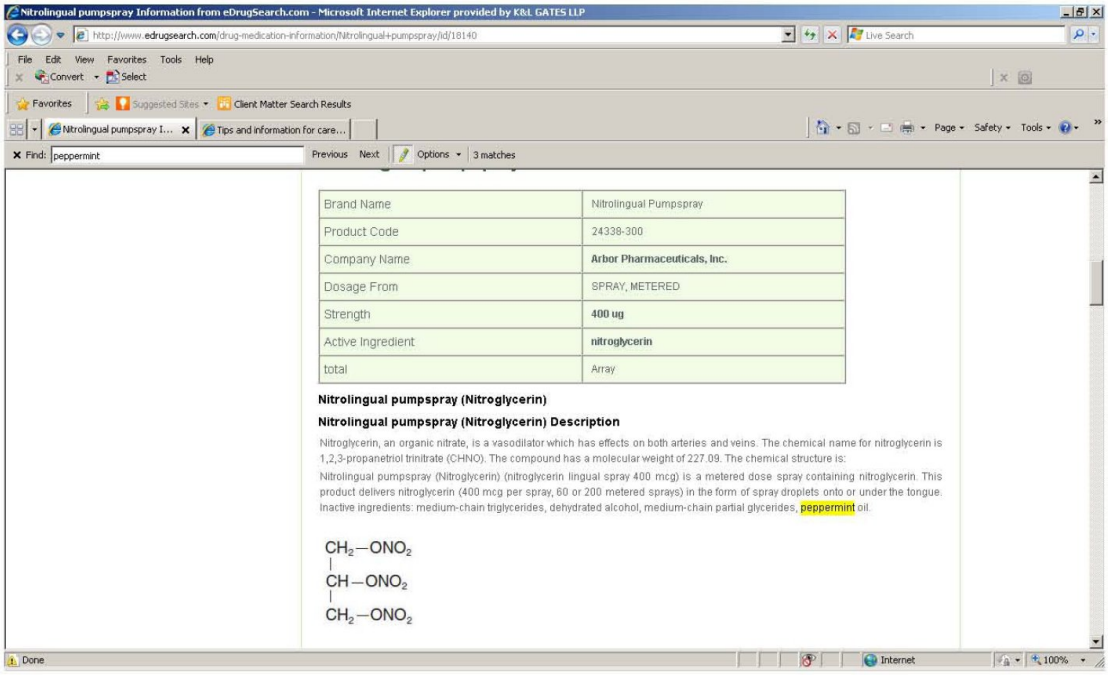

Reviews nitrolingual pumpspray - Microsoft Internet Explorer provided by K&L GATES LLP
http://www.reviewsaz.com/reviews_nitrolingual_pumpspray.html
File Edit View Favorites Tools Help
Convert Select
Favorites Suggested Sites Client Matter Search Results
Acquiring a Flavor For Trad... The taste of ripe strawberr... Reviews nitrolingual pu... Junior user trademark - Go... generic nitroglycerin - Goo...
Page Safety Tools
Find: peppermint Previous Next Options
fast, slow, pounding, or uneven heart rate;
blurred vision or dry mouth;
nausea, vomiting, sweating, pale skin, feeling like you might pass out; or
fever, sore throat, and...
Read All Potential Side Effects for Nitrolingual Pumpspray »
Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate (C3H5N3O9). The compound has a molecular weight of 227.09. The chemical structure is:
Nitrolingual® Pumpspray (nitroglycerin lingual spray 400 mcg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.Last reviewed on RxList: 11/3/2008
Nitrolingual Pumpspray Drug Description
Nitrolingual® Pumpspray
(nitroglycerin lingual) Spray 400 mcg per spray, 60 or 200 Metered Sprays
DRUG DESCRIPTION
What are the possible side effects of nitroglycerin (Nitrolingual, Nitrolingual Duo Pack, Nitroquick, Nitrostat)?
Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficulty breathing; swelling
Actiq Drug Description ACTIQ® (fentanyl citrate) Oral Transmucosal Lozenge WARNING IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE Reports of serious adverse events, including deaths in patients treated ...
Read More | Review This
Reviews Methsuximide
Celontin Drug Description Celontin® (methsuximide) Capsules, USP DRUG DESCRIPTION What are the possible side effects of methsuximide (Celontin)? Get emergency medical help if you have any of these signs of an allergic reaction: ...
Read More | Review This
Reviews Dht
Dht Drug Description DHT™ Tablets (Dihydrotachysterol Tablets USP): 0.125mg, 0.4mg DRUG DESCRIPTION What are the possible side effects of dihydrotachysterol (DHT, DHT Intensol, Hytakerol)? Get emergency medical help if you...
Read More | Review This
Reviews Tricarbocyanine
Ic-Green Drug Description IC-GREEN™ (Indocyanine Green for Injection, USP) Sterile DRUG DESCRIPTION IC-GREEN™ is a sterile, lyophilized green powder containing 25 mg of indocyanine green with no more than 5 % sodium iodide....
Done
Internet 100%


Nitrolingual pumpspray Information from eDrugSearch.com - Microsoft Internet Explorer provided by K&L GATES LLP
http://www.edrugsearch.com/drug-medication-information/Nitrolingual+pumpspray/id/18140
Find: peppermint
Previous Next Options 3 matches
Brand Name | Nitrolingual Pumpspray
Product Code | 24338-300
Company Name | Arbor Pharmaceuticals, Inc.
Dosage From | SPRAY, METERED
Strength | 400 ug
Active Ingredient | nitroglycerin
total | Array
Nitrolingual pumpspray (Nitroglycerin)
Nitrolingual pumpspray (Nitroglycerin) Description
Nitroglycerin, an organic nitrate, is a vasodilator which has effects on both arteries and veins. The chemical name for nitroglycerin is 1,2,3-propanetriol trinitrate (CHNO). The compound has a molecular weight of 227.09. The chemical structure is:
Nitrolingual pumpspray (Nitroglycerin) (nitroglycerin lingual spray 400 mcg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.
CH2—ONO2
CH—ONO2
CH2—ONO2
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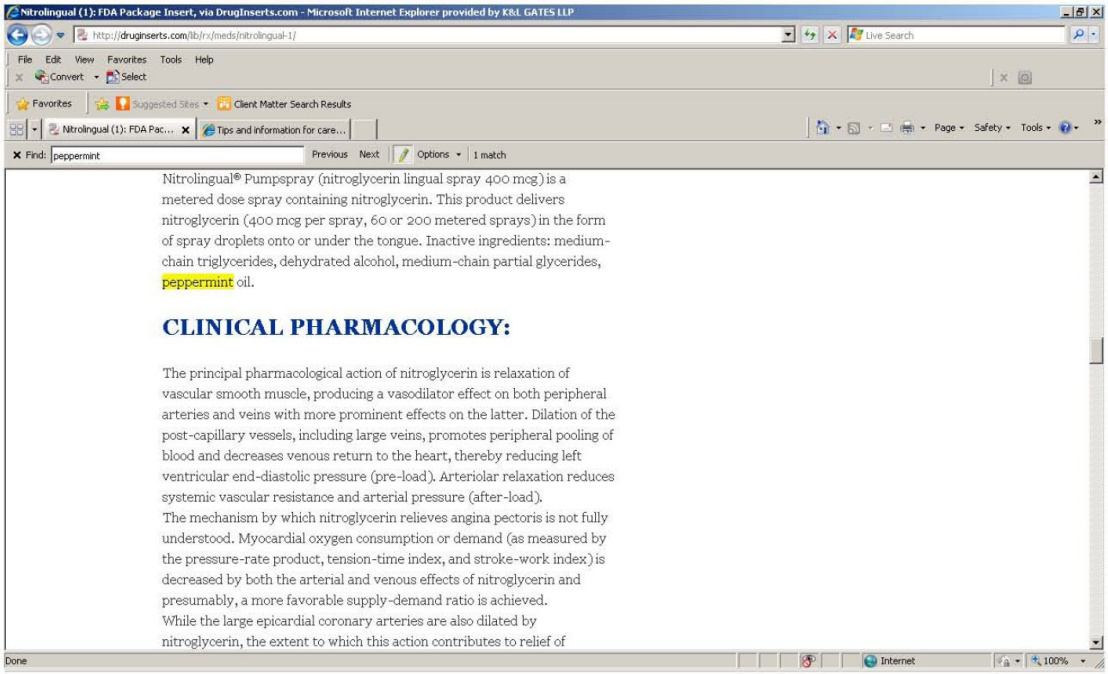
Nitrolingual (1): FDA Package Insert, via DrugInserts.com - Microsoft Internet Explorer provided by K&L GATES LLP
http://druginserts.com/lib/rx/meds/nitrolingual-1/
Find: peppermint
Previous Next Options 1 match
Nitrolingual® Pumpspray (nitroglycerin lingual spray 400 mcg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.
CLINICAL PHARMACOLOGY:
The principal pharmacological action of nitroglycerin is relaxation of vascular smooth muscle, producing a vasodilator effect on both peripheral arteries and veins with more prominent effects on the latter. Dilation of the post-capillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (after-load).
The mechanism by which nitroglycerin relieves angina pectoris is not fully understood. Myocardial oxygen consumption or demand (as measured by the pressure-rate product, tension-time index, and stroke-work index) is decreased by both the arterial and venous effects of nitroglycerin and presumably, a more favorable supply-demand ratio is achieved.
While the large epicardial coronary arteries are also dilated by nitroglycerin, the extent to which this action contributes to relief of
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Nitrolingual Pump Spray

1. Name Of The Medicinal Product

Nitrolingual Pumpspray

2. Qualitative And Quantitative Composition

Each metered dose contains 400 micrograms glyceryl trinitrate.

3. Pharmaceutical Form

Sublingual spray.

4. Clinical Particulars

4.1 Therapeutic Indications

For the treatment and prophylaxis of angina pectoris and the treatment of variant angina.

4.2 Posology And Method Of Administration

Adults and the Elderly:

At the onset of an attack or prior to a precipitating event: one or two 400 microgram metered doses sprayed under the tongue. It is recommended that no more than three metered-doses are taken at any one time and that there should be a minimum interval of 15 minutes between consecutive treatments.

For the prevention of exercise induced angina or in other precipitating conditions: one or two 400 microgram metered doses sprayed under the tongue immediately prior to the event.

Children:

Nitrolingual Pumpspray is not recommended for use.

Administration:

The bottle should be held vertically with the valve head uppermost. If the pump is new, or has not been used for a week or more, the first actuation should be released into the air. The spray orifice should then be placed as close to the mouth as possible. The dose should be sprayed under the tongue and the mouth should be closed immediately after each dose. The spray should not be inhaled. Patients should be instructed to familiarise themselves with the position of the spray orifice, which can be identified by the finger rest on the top of the valve, in order to facilitate orientation for administration at night. During application the patient should rest, ideally in the sitting position.

4.3 Contraindications

Hypersensitivity to nitrates or any constituent of the formulation. Hypotension, hypovolaemia, severe anaemia, cerebral haemorrhage and brain trauma, mitral stenosis and angina caused by hypertrophic obstructive cardiomyopathy. Concomitant administration of phosphodiesterase inhibitors used for the treatment of erectile dysfunction (section 4.5).

4.4 Special Warnings And Precautions For Use

Any lack of effect may be an indicator of early myocardial infarction.

As with all glyceryl trinitrate preparations, use in patients with incipient glaucoma should be avoided.

4.5 Interaction With Other Medicinal Products And Other Forms Of Interaction

Tolerance to this drug and cross tolerance to other nitrates may occur. Alcohol may potentiate any hypotensive effect.

The hypotensive effects of nitrates are potentiated by concurrent administration of phosphodiesterase inhibitors used for the treatment of erectile dysfunction. A severe and possibly dangerous fall in blood pressure may occur. This can result in collapse, unconsciousness and paradoxical myocardial ischaemia and may be fatal. Such use is therefore contra-indicated (section 4.3)

If a patient treated with these drugs for erectile dysfunction needs a rapidly effective nitrate, he/she should be closely monitored.

4.6 Pregnancy And Lactation

Nitrolingual Pump spray is not generally recommended and should be used only if its potential benefit justifies any potential risk to the foetus or neonate.

4.7 Effects On Ability To Drive And Use Machines

Only as a result of hypotension.

4.8 Undesirable Effects

Headache, dizziness, postural hypotension, flushing, tachycardia and paradoxical bradycardia have been reported.

4.9 Overdose

Signs and symptoms:

Flushing, severe headache, a feeling of suffocation, hypotension, fainting, restlessness, blurred vision, impairment of respiration, bradycardia and rarely, cyanosis and methaemoglobinaemia may occur. In a few patients there may be a reaction comparable to shock with nausea, vomiting, weakness, sweating and syncope.

Treatment:

Recovery often occurs without special treatment. Hypotension may be corrected by elevation of the legs to promote venous return. Methaemoglobinaemia should be treated by intravenous methylene blue.

Symptomatic treatment should be given for respiratory and circulatory defects in more serious cases.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Glyceryl trinitrate relieves angina pectoris by reduction of cardiac work and dilation of the coronary arteries. In this way, not only is there a lessening in arterial oxygen requirement but the amount of oxygenated blood reaching the ischaemic heart is increased.

5.2 Pharmacokinetic Properties

The pharmacokinetics of glyceryl trinitrate are complex; venous plasma levels of the drug show wide and variable fluctuations and are not predictive of clinical effect. In a human pharmacodynamic study, pharmacological activity had commenced one minute after dosing and was obvious by two minutes.

5.3 Preclinical Safety Data

None stated.

6. Pharmaceutical Particulars

6.1 List Of Excipients

Fractionated coconut oil, ethanol (absolute), medium chain partial glycerides, peppermint oil.

6.2 Incompatibilities

Not known.

6.3 Shelf Life

3 years.

6.4 Special Precautions For Storage

Do not store above 25°C.

6.5 Nature And Contents Of Container

Red plastic coated glass bottle fitted with metering pump. Each bottle contains 4.9, 11.2 or 14.2g solution (equivalent to about 75, 200 or 250 doses). Nitrolingual Pumpspray Duo pack contains a 4.9g and a 14.2g bottle.

6.6 Special Precautions For Disposal And Other Handling

See 'Administration' section.

7. Marketing Authorisation Holder

Merck Serono Ltd

Bedfont Cross

Stanwell Road

Feltham

Middlesex

TW14 8NX

UK

8. Marketing Authorisation Number(S)

PL 11648/0082

9. Date Of First Authorisation/Renewal Of The Authorisation

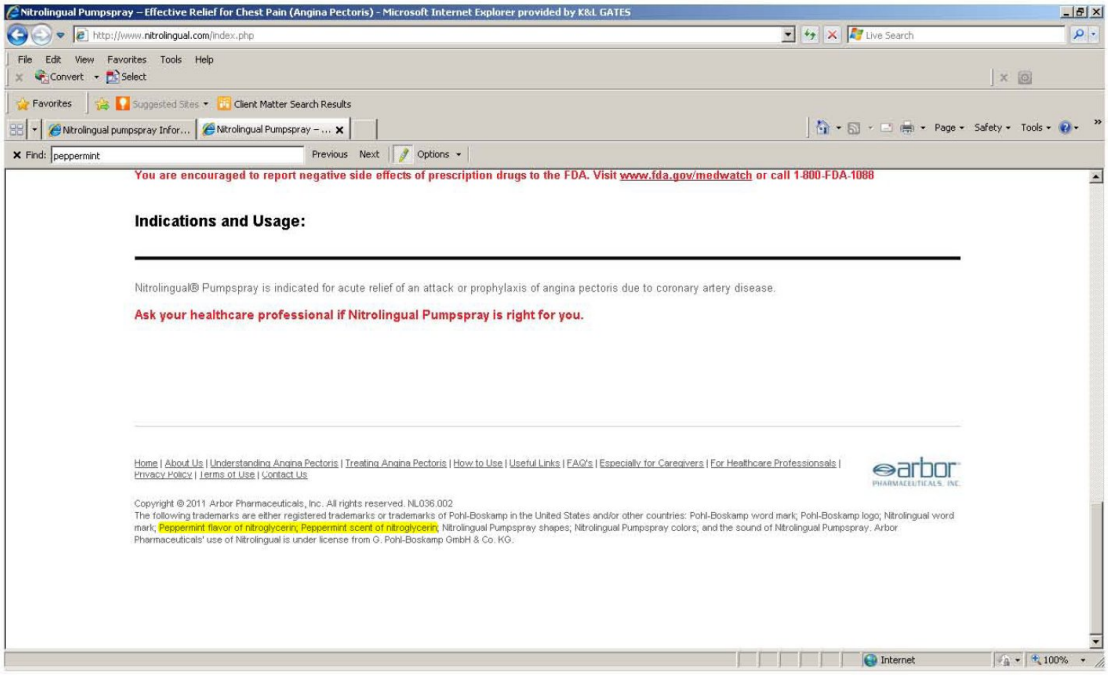
28 November 2005

10. Date Of Revision Of The Text

22nd January 2010

LEGAL CATEGORY Pharmacy

EXHIBIT E


Nitrolingual Pumpspray – Effective Relief for Chest Pain (Angina Pectoris) - Microsoft Internet Explorer provided by K&L GATES
http://www.nitrolingual.com/index.php
Live Search
File Edit View Favorites Tools Help
Convert Select
Favorites Suggested Sites Client Matter Search Results
Nitrolingual pumpspray Infor... Nitrolingual Pumpspray – ...
Page Safety Tools
Find: peppermint Previous Next Options
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088
Indications and Usage:
Nitrolingual® Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.
Ask your healthcare professional if Nitrolingual Pumpspray is right for you.
Home | About Us | Understanding Angina Pectoris | Treating Angina Pectoris | How to Use | Useful Links | FAQ's | Especially for Caregivers | For Healthcare Professionals | Privacy Policy | Terms of Use | Contact Us
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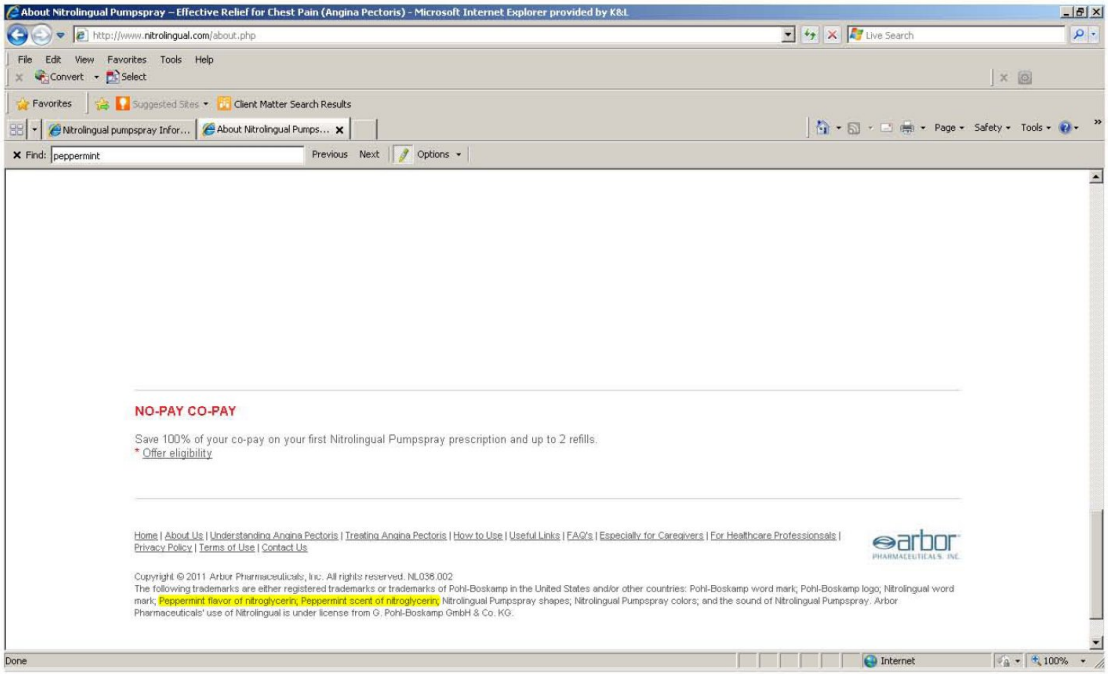
About Nitrolingual Pumpspray – Effective Relief for Chest Pain (Angina Pectoris) - Microsoft Internet Explorer provided by K&L
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Live Search
File Edit View Favorites Tools Help
Convert Select
Favorites Suggested Sites Client Matter Search Results
Nitrolingual pumpspray Infor... About Nitrolingual Pumps...
Page Safety Tools
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Save 100% of your co-pay on your first Nitrolingual Pumpspray prescription and up to 2 refills.
* Offer eligibility
Home | About Us | Understanding Angina Pectoris | Treating Angina Pectoris | How to Use | Useful Links | FAQ's | Especially for Caregivers | For Healthcare Professionals | Privacy Policy | Terms of Use | Contact Us
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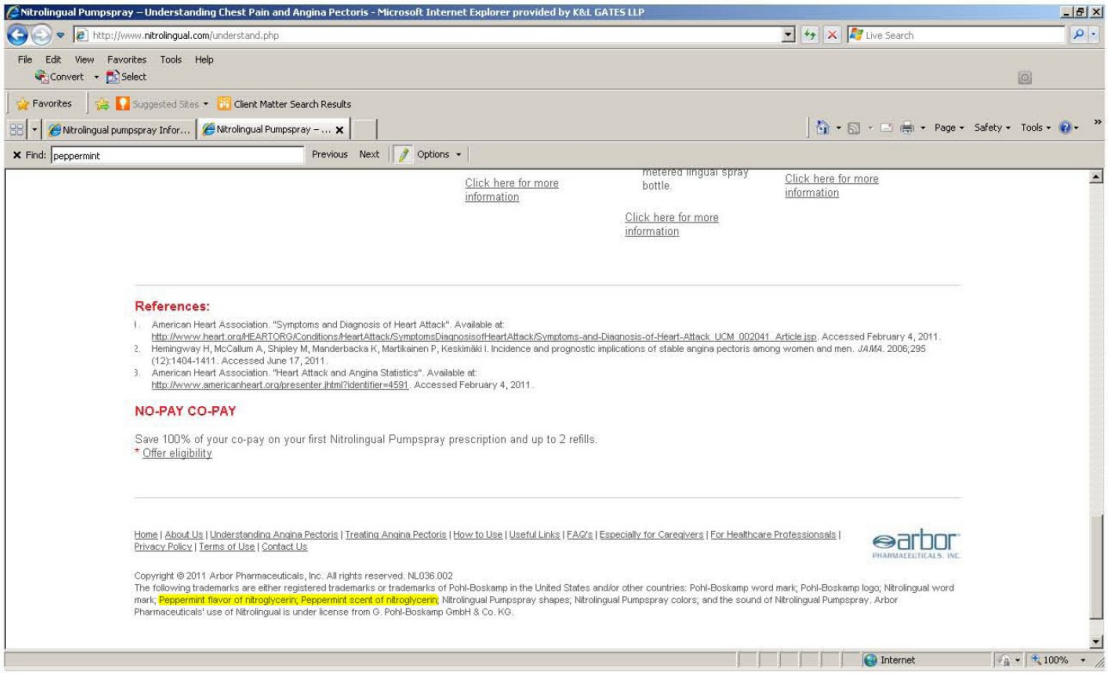
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metered lingual spray bottle.
Click here for more information
Click here for more information
References:
1. American Heart Association. "Symptoms and Diagnosis of Heart Attack". Available at: http://www.heart.org/HEARTORG/Conditions/HeartAttack/SymptomsDiagnosisofHeartAttack/Symptoms-and-Diagnosis-of-Heart-Attack_UCM_002041_Article.jsp. Accessed February 4, 2011.
2. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and prognostic implications of stable angina pectoris among women and men. JAMA. 2006;295 (12):1404-1411. Accessed June 17, 2011.
3. American Heart Association. "Heart Attack and Angina Statistics". Available at: http://www.americanheart.org/presenter.jhtml?identifier=4591. Accessed February 4, 2011.
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* Offer eligibility
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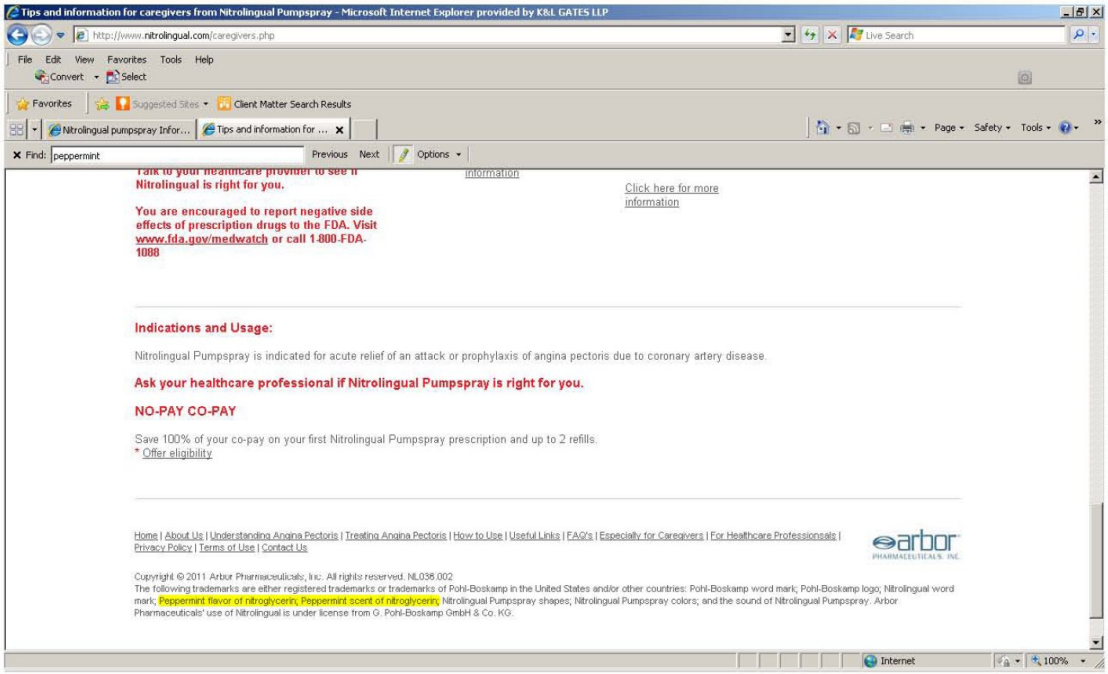
Tips and information for caregivers from Nitrolingual Pumpspray - Microsoft Internet Explorer provided by K&L GATES LLP
http://www.nitrolingual.com/caregivers.php
Talk to your healthcare provider to see if Nitrolingual is right for you.
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088
Click here for more information
Indications and Usage:
Nitrolingual Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.
Ask your healthcare professional if Nitrolingual Pumpspray is right for you.
NO-PAY CO-PAY
Save 100% of your co-pay on your first Nitrolingual Pumpspray prescription and up to 2 refills.
* Offer eligibility
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Reliable angina relief –
Nitrolingual® Pumpspray
(nitroglycerin lingual spray)

Fire extinguisher image does not depict actual product.

Stability & Potency

Rapid Pain Relief

Ease of Use

Indications and Usage Nitrolingual® Pumpspray is indicated for acute relief of an attack or prophylaxis of angina pectoris due to coronary artery disease.

Important Safety Information Nitrolingual Pumpspray should not be used while taking phosphodiesterase inhibitors which are used for the treatment of erectile dysfunction. Nitrolingual Pumpspray should be used with caution if patients have low systolic blood pressure, are undergoing diuretic therapy, or show hypersensitivity to this and other nitrates or nitrites. Headache is the most commonly reported side effect with nitroglycerin. Patients may also experience episodes of dizziness, weakness, and other related side effects.

Nitrolingual® Pumpspray
(nitroglycerin lingual spray)
0.4 mg nitroglycerin per spray

PROVEN TRUSTED RELIABLE WWW.NITROLINGUAL.COM

WWW.NITROLINGUAL.COM

Please see full Prescribing Information on next page.

NL.001.01

EXHIBIT D

Whois Record For NitroLingual.com

Tweet

Whois Record | Site Profile | Registration | Server Stats | My Whois

Reverse Whois: "Pohl-Boskamp GmbH & Co." owns about 9 other domains

Email Search: domreg@tng.de is associated with about 4,936 domains

info@pohl-boskamp.de is associated with about 65 domains

Registrar History: 2 registrars with 2 drops.

NS History: 2 changes on 3 unique name servers over 9 years.

IP History: 4 changes on 4 unique IP addresses over 7 years.

Whois History: 30 records have been archived since 2001-09-04 .

Reverse IP: 2 other sites hosted on this server.

Log In or Create a FREE account to start monitoring this domain name

DomainTools for Windows®
Now you can access domain ownership records anytime, anywhere... **right from your own desktop!** Download Now>

```
Registrant:
  Pohl-Boskamp GmbH & Co. (POHLBOSK116)
  Kieler Str. 11

  Hohenlockstedt, Schleswig-Holstein, 25551
  DE

  Domain name: nitrolingual.com

Technical contact:
  Puerwitz, Arne (AP1025)
  TNG - THE NET GENERATION AG
  Projensdorfer Str. 324

  Kiel, 24106
  DE
  domreg@tng.de
  +49.431709710 Fax: +49.4317097555

Administrative contact:
  Ohlen, Susanne (SO92)
  G. Pohl-Boskamp GmbH & Co.
  Kieler Str. 11

  Hohenlockstedt, Schleswig-Holstein, 25551
  DE
  info@pohl-boskamp.de
  +49.4826590 Fax: +49.482659109

Record created:          2004-03-22 14:36:49
Record last updated:     2011-03-29 16:48:47
Record expires:          2012-09-03 00:00:00

Domain servers in listed order:
  ns1.bluehost.com (NSBLUEHO102)
  ns2.bluehost.com (NSBLUEHO763)
```

Country TLDs | General TLDs

Available domains for registration:

NitroLingual.be	Register
NitroLingual.ch	Register
NitroLingual.cn	Register
NitroLingual.dk	Register
NitroLingual.es	Register
NitroLingual.in	Register
NitroLingual.it	Register
NitroLingual.jp	Register
NitroLingual.mx	Register
NitroLingual.pl	Register

Register All Selected > Show all (12) >